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ISLET CELL TUMORS OF THE PANCREAS.*

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In 1927, Wilder,[9] with others, reported the case history of a physician who noted sudden attacks of weakness, faintness and paraesthesia, progressively increasing in severity and causing trembling and profuse sweating. The attacks were controlled by carbohydrate administration, but soon it became necessary to feed him even while asleep. Metabolic studies disclosed hypoglycemia and at operation, resorted to in the hope of providing relief, a tumor of the pancreas with metastases in the liver was discovered. At pathologic examination this was shown to be a malignant islet cell tumor and insulin was found in a liver metastasis. This brilliant diagnosis from complete clinical and pathologic studies firmly established the disease hyperinsulinism which had been postulated by Seale Harris[1] in 1923 and subsequently supported by reports of its minor forms. Previously some 20 cases of islet cell tumor, diagnosed pathologically, had been reported but no clinical correlation had been established. More recent investigations show an incidence of such tumors in 1 of 800 or 1000 autopsies, but related symptoms have been described in only 20% of these cases.

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In the year following Wilder's report, McClenahan and Norris,[3] and Thalhimer and Murphy[5] described somewhat similar symptoms in patients who, at autopsy, were found to have an islet cell tumor of the pancreas, and some months later we[2] had the opportunity to study such a case and to remove an islet cell carcinoma with entire and permanent relief of symptoms. Since that time the number of cases recognized and successfully treated or identified at necropsy has grown to somewhat less than 100. The most extensive series is that of Whipple[7] who has reported 11 cases; most publications concern individual cases. The subject has been carefully reviewed by Sigwald[4] in France, by Wauchope[6] in England and by Whipple,[8] Womack[10] and others in America.

In our first report it was necessary to leave in abeyance the question of cure since the tumor possessed characteristics of malignancy and, though careful search did not disclose any metastases, it could not be definitely asserted that they would not later make their appearance. Now, more than 10 years later, the patient is in good health and without any evidence that metastatic tumors, such as occurred in Wilder's and other cases, have developed. It should also be said that this patient has remained free of any disability related to the uncontrolled over-production of insulin for which she was treated by surgical operation. In each of these respects, then, it seems reasonable to assume a cure of the condition. In the intervening time, among other cases of spontaneous hyperglycemia encountered, we have been able to study 3 additional patients from whom an islet cell tumor has been removed as well as a patient with persistent and severe diffuse hyperinsulinism who has obtained complete relief from her disability for a period of 10 months following resection of a large part of the pancreas. These cases will be reported briefly here.

Case Reports. Case 1.—A female, aged 52 complained of exhaustion in September, 1922, then feeling ill she threw herself on the bed and gradually became comatose. She was restless, tossed about, grimaced and failed to comprehend questions. Sweating and vomiting occurred. Consciousness returned in an hour but the feeling of exhaustion persisted. Similar attacks were experienced 6 times within the next 2 years and from then on they increased in duration, frequency and severity. After it was noted that food would abort an attack, frequent lunches were adopted as regular treatment but later they seemed to lose their effect. Attacks became more frequent and the comatose state more prolonged; convulsions, incontinence and temporary hemiplegia sometimes occurred.

The patient's general physical condition was not abnormal except for her carbohydrate metabolism. During an attack blood sugars were at severe hypoglycemic levels. A blood sugar tolerance curve was of the diabetic type, but excessive amounts of sugar usually provoked hypoglycemia. Epinephrin caused hyperglycemia. Varying the rate and amount of carbohydrate intake permitted production and some restraint of symptoms, but proved to be an unreliable and erratic mode of control. Continued frequent dosage with small amounts of carbohydrate by mouth would keep the patient in a normal condition for considerable periods but, on the other hand, the

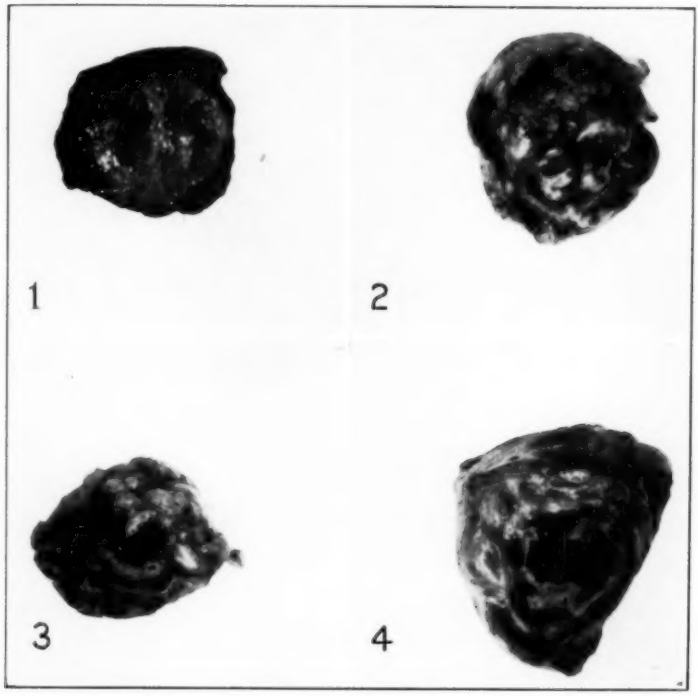

FIG. 1.—Four islet cell tumors. Gross appearance, showing relative size.

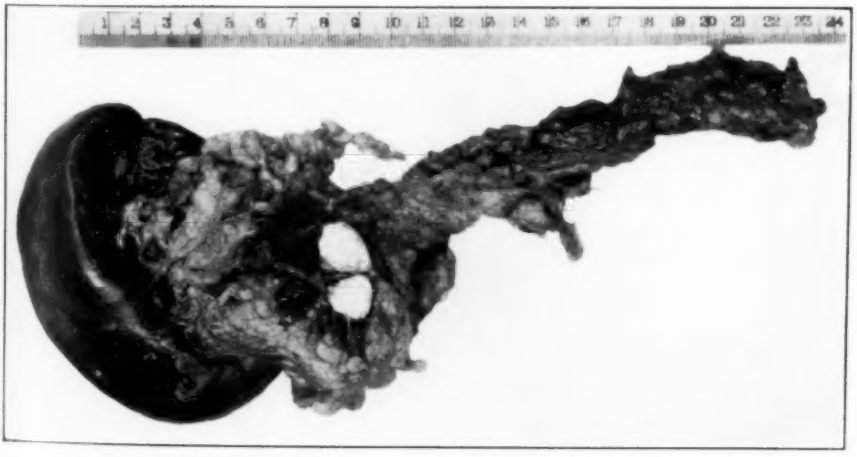

FIG. 2.—*Case 4.*—The islet tumor *in situ*, sectioned and turned back. Note the grayish-white color of the growth in contrast to the normal surrounding pancreatic tissue.

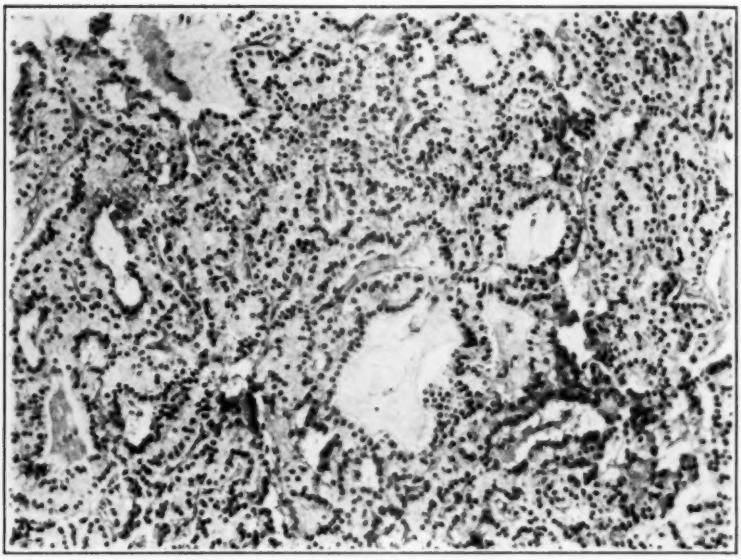

FIG. 3.—*Case 2.*—A benign tumor growth composed of small cells with deeply stained nuclei arranged in an alveolar manner. These cells were predominantly of the Alpha type. (× 75.)

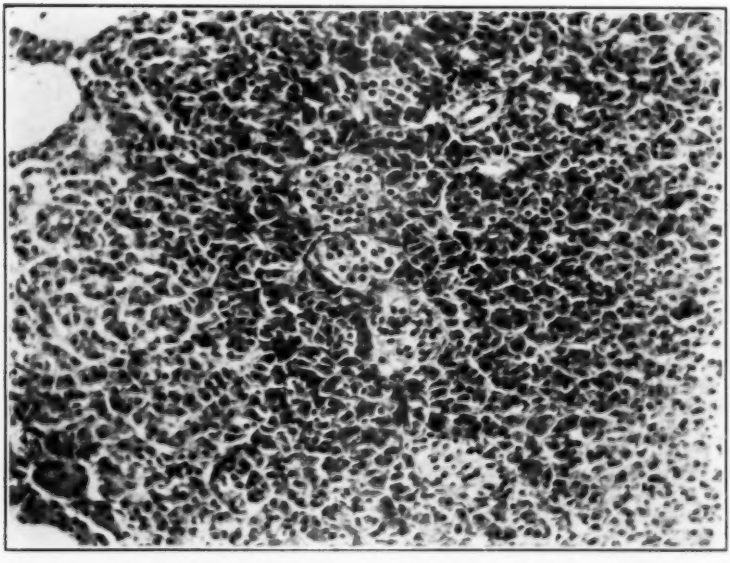

FIG. 4.—*Case 5.*—The marked increase in the number of islets is illustrated here by the presence of five in one field. While the islets are small, the individual cells are hypertrophied and have deeply staining nuclei.

dose of carbohydrate administered to cure one attack sometimes appeared to provoke another. With Wilder's case in mind, operation was advised and one of us removed an islet cell tumor from the body of the pancreas. A fibrous pseudo-capsule, invaded in places by tumor tissue, separated the normal-appearing surrounding pancreas from the tumor mass which showed large cells arranged in cords and in masses with little stroma. The nuclei varied considerably in size. Using special stains, granules of the Beta cell type were demonstrated in 20% of the cells; in most of the remaining cells both types of granules appeared in the same cell. In some places, pancreatic ducts were found embedded in a dense fibrous connective tissue stroma. Through the kind coöperation of Prof. Best, Dr. D. A. Scott analyzed this and also specimens obtained from later cases. Insulin was found but, in this case, the examination was not quantitative since his present method for determining insulin in small quantities had not been developed.

CASE 2.—A woman, aged 25, in the third month of pregnancy (April, 1934), had 5 epileptiform attacks in 3 days, mostly in the early hours of the morning. The seizures were characterized by muscle twitchings, incoördinate movements and loss of consciousness. Twenty-eight days after confinement the patient experienced another attack similar in character but with numbness in lips, hands and feet, extreme weakness and vertigo at onset. For a time, attacks occurred daily; later, they became less frequent. She could not be roused for the 2 A.M. or 6 A.M. feeding of the baby. Some improvement was noted with administration of ephedrine but this soon ceased to be effective. The baby was weaned and following this the patient had fewer attacks for some time. With each menstrual period, however, attacks recurred and, besides the more severe ones, there were periods when numbness of the lips interfered with speech, when she became drowsy, clumsy or "lazy," and showed lack of interest and emotional blunting.

The patient was admitted to hospital on July 30, 1935. A series of generalized convulsions occurred at about 5 A.M. on August 1 and succeeding days. Blood sugar levels during these attacks were usually around 0.04%. Delaying food provoked attacks and complete relief was obtained by glucose administration. A blood sugar tolerance test was of the diabetic type, with marked glycosuria. A general physical examination revealed nothing of importance save a moderate reduction in weight. On Roentgen-ray examination the skull was normal.

The introduction of carbohydrate meals at 11 P.M. and 4 A.M. appeared to control the attacks for a time but gradually became less effective. Operation was advised and undertaken. After careful search and no tumor found, a resection of all the pancreas to the left of the inferior mesenteric artery was carried out. The excised pancreas showed hyperplastic islands and four times the normal insulin content. From a surgical standpoint the patient made a good recovery; no attacks appeared in the 15 days following operation. This period of freedom from attacks, we now believe, was due to the post-operative diet which was rather high in carbohydrates. Attacks of marked severity then occurred and some considerable study of various dietary regimens led us to prescribe a diet with added carbohydrate to cover the probable periods of hypoglycemia. On this diet the patient remained relatively free of attacks, but because of an increase of 90 pounds in weight she attempted to diminish her diet; the attacks recurred and the patient returned to our care in January, 1938. In view of the possibility that a tumor had remained undiscovered at the first operation, it seemed advisable to re-explore the pancreas. After mobilizing the second portion of the duodenum, a tumor was palpated in the head of the pancreas and removed with some little difficulty because of hemorrhage. The tumor tissue consisted of small cells with deeply stained nuclei arranged in cords and alveoli. A majority of the cells contained granules of the Alpha type, and

the insulin content was found to be approximately 8 times that of normal pancreatic tissue. Under dietary restriction the patient lost her excess weight; blood sugar tolerance tests gradually became normal and she has been on ordinary diet for the past year. During the 20 months following the second operation she has felt well and there has been no evidence of recurrence of hypoglycemia.

Case 3.—A woman, aged 47, 3 days following parturition in 1934, had numbness about the mouth for 3 days. It then became more widespread, with mental confusion and loss of memory. In August, 1935, she had generalized convulsions and by March, 1936, similar attacks occurred almost daily, but ceased during pregnancy—May to July, 1936. Miscarriage occurred and the attacks returned. In a later pregnancy, there were only two such episodes until the ninth month when a severe convulsive seizure occurred, lasting 8 hours. Pregnancy was terminated and daily attacks followed.

The patient was brought to hospital unconscious, *in status epilepticus*. Her health otherwise had been good but her husband had noted an increasing mental dullness and emotional instability. There was a moderate sized colloid goiter, otherwise the physical examination revealed nothing abnormal except during the convulsive periods when opisthotonus, spasticity, increased reflexes and bilateral Babinski phenomenon occurred. The blood sugar was .033%. Glucose given intravenously stopped the convulsions; the patient opened her eyes, followed a light and seemed to understand but could not speak. In an hour, she answered questions slowly and inarticulately and obeyed commands. The following day she had several seizures which were relieved by glucose. The next day a glucose tolerance test showed notably low values throughout. It seemed impossible to raise the blood sugar above the normal level by glucose given simultaneously by the intravenous route and by duodenal drip, so further investigation was abandoned and operation advised.

At operation, which was carried out under a spinal anesthetic, a tumor was palpated deep in the head of the pancreas and excised. The change was dramatic. In 15 minutes following the removal of the tumor the patient roused and attempted to speak. Her pale, clammy skin dried and breathing became normal.

The tumor was made up of cells, some of which had a clear cytoplasm, others having fine granules. The nuclei, for the most part, were small and deeply stained. Using Bowie's stain, some 80% of the cells showed granules of the Beta type. The insulin content of the tumor was 85 units per gm., about 40 times the amount found in normal human pancreatic tissue.

Following operation the patient seemed to improve temporarily. The blood sugar level remained continuously in the normal zone, and a blood sugar tolerance test was nearly normal. However, she gradually became more confused mentally, more restless (required restraint), incontinent, ceased to recognize people, lost any understandable speech, and developed increased reflexes, muscle wasting, aphasia and incoördination. Measures of reëducation were undertaken and gradual improvement has taken place over the last 15 months but she is still unstable emotionally, irritable, her memory is poor, and dysarthria is quite marked. She has gained in weight, the muscle wasting in the hands is much improved, but coördination is not good. She feeds herself with difficulty, is unable to walk without assistance and requires help with dressing. Fasting blood sugar levels, as well as the blood sugar tolerance test, are now normal. There have been no further hypoglycemic attacks.

Case 4.—This patient is a woman, aged 46. It is possible that the first symptoms of her illness occurred 8 years ago, when it was noticed that she was somewhat irritable, became hysterical in behavior, then moody and,

subsequently, remembered little of her actions. She was well apparently for 2 years; then these symptoms recurred. Within a short period she had several attacks which were recognized as hypoglycemic in origin and carbohydrate was prescribed for their relief. Though this treatment was satisfactory for a time, her friends noticed that she became careless in dress, speech and behavior and antagonized people by her comments and actions. It is not improbable that many of these incidents took place while she was in an unrecognized state of mild hypoglycemia, but it seems certain that there was considerable alteration in character apart from the attacks. She felt moody, sullen and irritable most of the time. At first there was a gradual, then a rapid increase in the frequency and severity of the attacks until it became necessary to administer 20 gm. of glucose every hour and a half during the day, in addition to meals, and every 2 hours during the night to prevent unconsciousness. On this routine she became extremely obese and applied for relief because of this, as well as because of the increasing severity of her attacks.

The patient was admitted to hospital and, in spite of 45 gm. of glucose administered at 12, 2,30 and 5 A.M., respectively, a 7.30 A.M. estimation of blood sugar was .037%. This rose in 30 minutes, after administration of 100 gm. of glucose, to .075% and in 2 hours had gradually reached .090%, from which point it declined until at 4.30 P.M. it was .040% and definite signs of hypoglycemic reaction were present. Her general physical condition was normal except for the obesity. The sella turcica was normal. The metabolic rate shortly after sugar administration was +12%. On examination, urine and blood were normal.

Operation was advised and undertaken but was difficult on account of the amount of fat surrounding the organs. A tumor was found in the tail of the pancreas, but splenectomy and partial resection of the pancreas were necessary. Though febrile following operation, the patient felt well apart from a sensation of distention of the abdomen. The blood sugar came down to normal when the intravenous glucose was discontinued. On the third day her temperature rose suddenly to 107° F., accompanied by a corresponding rise in pulse and respiratory rate and she died in 3 hours. We were unable to discover the cause of the sudden hyperthermia and necropsy was not permitted. Ziskind[12] has recorded a similar case.

The tumor weighed 3.4 gm. and was enclosed in a definite capsule. It consisted of rounded and cord-like masses of cells with a granular cytoplasm, 98% of which showed Beta granules. The adjacent pancreatic tissue removed with the tumor showed a great increase in the number and size of islets. The insulin content of the pancreas was 1.9 units per gm. of tissue, while that of the tumor was 4 times as great.

CASE 5.—A woman, aged 22, was kindly referred by Dr. E. F. Brooks of St. Michael's Hospital. This patient was well until February, 1935, when, following an attack of influenza, jaundice occurred and, with recovery, she commenced to complain of excessive fatigue. Great exhaustion followed mild exercise. In June, 1936, she had a convulsion in a motor car. A short time later, her parents, returning home, found her unconscious. She had probably been so for 8 hours when her physician arrived and, suspecting a hypoglycemic state, administered glucose; she regained consciousness in 10 minutes. Such episodes were repeated whenever she went too long without food or indulged in any exercise. On several occasions blood sugars were found to be 0.02 to 0.03%. Provoked attacks gave similar values. A glucose tolerance test was of the diabetic type. Diet proved ineffective in controlling the attacks of hypoglycemia and operation was recommended.

On November 14, 1938, the pancreas was carefully examined but no evidence of tumor was revealed. As other possible causes of the hypoglycemia could reasonably be ruled out, a resection of 34 gm. of the pancreas was

carried out, leaving a mass of pancreatic tissue of approximately 1 by 2 cm. Though the patient later developed an empyema requiring drainage in February, 1939, she has remained free of all attacks; numerous blood sugar estimations all have been within normal limits during the 10 months since operation, and no glycosuria has occurred on normal diets.

Though no tumor was found in this case, there were large numbers of islets in the pancreas (5 per low power field), which were made up of very large cells with deeply-staining nuclei. This probably explains the hyperinsulinism. The insulin content of the tissue was normal.

TABLE 1.—CASES OF HYPERINSULINISM.

Case.	Tumor.			Insulin content units per gm.	Cell type.	Result of operation.
	Color.	Weight gm.	Position.			
1	Red	0.84	Body	+	20 per cent β cells; remainder contained granules of both types. (Malignancy.)	Cured
2	A. Yellow pink	20.0	Tail	8	Hyperplastic islands.	Unimproved
	B. Maroon	2.25	Head	17	Majority α cells.	Cured
3	Maroon	1.3	Head	85	80 per cent β cells.	Cured
4	A. Yellow red	36.0	Tail	1.9	Increased number and size of islets of normal pancreas.	Cured
	B. Maroon	3.4	Tail	8	98 per cent β cells tending to infiltrate pancreas.	(Died)
5	Yellow pink	34.0	Tail	2	No tumor found. Islet tissue increased due to increase in islets but more to hypertrophy of individual cells.	

A—Pancreatic tissue.
B—Tumor tissue.
A normal pancreas weighs 60–100 gm., its islet tissue 1½% of this. Alpha and beta cells are approximately equal in number. The insulin content of the pancreas is 2 to 3 units per gram.

Discussion. Some of the salient facts in regard to these cases are collected in Table 1. Cases 1 and 2 appear to be cured. It seems important to remember that, though hyperplastic islands and increased insulin content of the pancreas may be present, their reduction by resection of a large portion of the pancreas may not provide a cure, as is illustrated in Case 2, though the happy outcome in Case 5, up to the present at least, provides some hope that this may take place, providing a sufficient volume of the pancreas is removed. Though many resections reported in the literature have been relatively unsuccessful, there are a few which have been followed by complete relief of symptoms; in most of the failures one suspects the removal of insufficient pancreatic tissue. But, even though marked hyperplasia be demonstrated, there can be no guarantee that a concealed tumor may not be the principal cause of

hyperinsulinism, as is illustrated in Case 2. In earlier reported cases re-operation has also proved successful in locating a tumor previously overlooked. The discovery of multiple adenomata in some cases makes it advisable to perform a second operation in any case which does not show a restoration of the carbohydrate metabolism to normal following the removal of an islet cell tumor. The necessary surgical procedures vary in the individual case. Since the tumor mass is small and may be entirely surrounded by normal pancreas, as it was in 2 of our cases, vision alone cannot be relied upon to locate it. Complete mobilization of the pancreas to permit adequate palpation is the absolute essential of the technical maneuver and, if the patient is obese, even then its discovery may not be easy. The mobilization must permit palpation between thumb and fingers of the head, body and tail of the pancreas. This is accomplished by dividing the peritoneum on the concavity and convexity of the first and second part of the duodenum. One can thus displace the head of the pancreas from under the mesenteric vessels and thoroughly palpate the whole structure. By dividing the peritoneum along the inferior border of the body and tail of the pancreas, this area may also be thoroughly palpated between the thumb and fingers.

In Case 3, the severe degree of damage sustained by the nervous system, as evidenced by incoördination of voluntary effort as well as by a changed mentality, as a result of the prolonged activity of the islet cell tumor, and the astonishing concentration of insulin in the tumor are worthy of note. Recovery from the injury is still progressing. The fourth case illustrates those alterations in character and mental outlook which are likewise causing concern in some of our unstable diabetics of long standing whose reactions to a certain dose of insulin are erratic and unpredictable. The obesity dependent upon increased carbohydrate intake complicates necessary surgical procedures.

In Case 5, an increased number of islets in the pancreas together with a hypertrophy of the individual cells, rather than an encapsulated tumor, appears to be the cause of a severe hyperinsulinism since, with resection of all but a portion of the pancreas measuring only 1 by 2 cm., a complete cessation of all symptoms occurred and has persisted for 10 months. This does not necessarily imply permanent cure any more than resection of a hyperactive goiter is always followed by permanent cure, nor is it entirely impossible that an overlooked adenoma may some day cause an explosion. However, isolated, severe attacks have seldom, if ever, occurred when the condition has become well established. The lapse of 10 months without any recurrence strongly suggests that the condition is adequately controlled.

Dietary regimens of various kinds have been tried in these cases. In our hands they have proved ineffective in controlling for long

the symptoms of severe hyperinsulinism. As 4 of our patients had islet cell tumors, perhaps this is not surprising. Better results might have been obtained in milder cases dependent upon a diffuse hyperplasia of islet cells.

Anterior lobe hypophyseal extracts of considerable effectiveness can now be obtained and some have even been tried in tumor cases. The effect of these extracts in animals has been shown to be exerted on the cells of normal islets. Unless a specific effect on tumor cells can be demonstrated, it might seem preferable to avoid such treatment in tumor cases, since there is little likelihood of affecting the tumor cells without at the same time destroying the normal insulin-producing units and thus producing diabetes plus erratic insulin release from the tumor cells. If a means of accurate clinical differentiation of the diffuse islet cell hyperplasia and the localized tumor mass could be devised, operation for the latter group and relative impairment of the islet tissue by hypophyseal extracts for the former might seem to be logical. But, as Dr. Young[11] has kindly pointed out, hypophyseal extracts operate on an all-or-none principle, insufficiently injured cells reverting to normal in a few days.

The insulin content of a normal human pancreas is approximately 150 units, or 6 mg. The actual production of insulin per day is much more difficult to determine and probably is dependent on the amount and composition of the diet, the antagonistic balance with other hormones, as well as on numerous other factors. Of much importance, however, is the delicate balance which is normally maintained between these various factors to permit of a normal concentration of sugar in the blood and tissues. In the presence of islet cell tumors both of these mechanisms are disturbed. The islet cells of tumors exceed the normal islet tissue of the whole human pancreas by one to four times and approximate that found in the principal islets of fishes. Regulation of insulin production and release may be disturbed by excessive production and continuous or erratic excessive release of insulin from these tumors which probably are not under the same measure of control as the normal islet tissue. In fact, the histories of these patients indicate that all of these factors may operate together or separately. The actual concentration of insulin found in the tumors is not to be regarded as an adequate measure of their activity, though it is interesting to note that it ranges between 4 and 40 times that of normal pancreas and nevertheless, in amount, is not equal to that of a normal pancreas. It should be stated that these values are applicable to the time of excision only, are not necessarily either maximal or minimal, and are not to be compared with concentrations found in normal tissue which may vary but within much narrower limits. The range of variation may depend upon differences in rate of production or storage or secretion, or a balance between these. On this account,

the amount of islet tumor tissue, the cell type and the insulin content of the tumor can only be related in a general way to the clinical expression of insulin overdosage. As they collaborate in varying degrees in releasing a noxious agent into the body, great differences may be expected in the symptomatology at various times, with but one feature in common—the general tendency to increase in severity as time passes.

Besides its dominant rôle in the production of symptoms of hyperinsulinism and excess insulin administration, hypoglycemia may be found playing a secondary, even an incidental rôle, in numerous other conditions. Among these, liver disturbances—tumor, atrophy, fatty infiltration, and poisoning caused by chloroform, phosphorus, arsenic or alcohol—and muscular dystrophy are associated with impaired glycogen metabolism; extreme fatigue and infections with excessive use of the available carbohydrate; lactation, pregnancy and renal glycosuria with abnormal drainage of the blood sugar; while a loss or damage to the normal antagonists, such as occurs in diseases of the thyroid, adrenal cortex and pituitary gland, accounts for another group of hypoglycemias. Imperfect adaptation to diet or perhaps some hyperactivity of the islet cells, particularly in children, may give rise to a condition of functional hyperinsulinism which is readily controllable by dietetic measures.

A study of the associated clinical symptoms in such cases will usually provide adequate differentiation. The past history of a case of islet cell tumor is one of minor attacks of exhaustion or fatigue followed by isolated episodes of more severe nature in which many of the well known symptoms of insulin overdosage may appear up to the stages of acute mania, unconsciousness or convulsions. Increasing frequency of attacks, together with the volunteered statement that ingestion of food relieves or totally inhibits an attack and a consequent development of obesity characterize the later course of the disease.

Signs of degeneration of the nervous system, analogous to those found in experimental insulin overdosage in animals, may appear relatively early and be accompanied by irritability, emotional instability, a loss of the finer attributes of character and reversion to vulgarity. Carelessness in speech, dress and deportment accompany these manifestations and, in later stages, may become irreversible characteristics. These developments, together with the technical difficulties incident upon obesity, make early diagnosis and removal of tumors desirable.

In attacks, the blood sugar is invariably low; repeated examinations to confirm this are necessary. There is a greater tendency for the attacks to occur a long time after food—in the early morning hours—or after exercise, and attacks may be provoked by deprivation of food or by the administration of small doses (5 units) of

insulin. It may be difficult to raise the blood sugar with glucose, or too much glucose may initiate another attack. In many cases the blood sugar tolerance test may be of the diabetic type. Dietary treatment may suffice for the milder cases of diffuse hyperplasia of islet cells, but it is doubtful if it has ever been effective for long in tumor cases.

The number of cases of true hyperinsulinism discovered in the past 10 years bears little relation to the incidence of islet cell tumors found at autopsy by careful examination. While it is true that in many instances such tumors need not be expected to produce well marked clinical symptoms, it also seems likely that careful review of patients suffering from nervous or mental disabilities, with islet cell tumor in mind, would yield a much larger harvest of these cases.

Summary. Four cases of islet cell tumor of the pancreas and one case of diffuse hyperplasia of islets with hypertrophy of islet cells are presented.

A varied clinical symptomatology, dependent on the hypoglycemia is shown, which parallels the results of experimental hyperinsulinism in animals. From the mildest of isolated episodes, the attacks run a course eventually resulting in marked mental deterioration and degeneration of the nervous system; marked obesity occurs as the disease progresses. Thus, early diagnosis and adequate treatment are especially desirable, not only to prevent the unfavorable later results but also to avoid the increased technical difficulties encountered in late operation. While, in mild diffuse hyperinsulinism, dietary treatment may suffice and the patient revert to normal, the process in tumor cases is progressive and nothing short of excision of the tumor will give the patient relief from his symptoms. The islet cells in these tumors exceed the mass of islet cells in the normal pancreas, and their insulin content is from 4 to 40 times that of the normal pancreas per gram, but not *in toto*. The clinical symptoms seem largely dependent upon uncontrolled secretory activity of the tumor rather than upon continuous production of excess quantities of insulin, until the later stages when the latter factor plays a larger rôle.

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SHOULD DIGITALIS BE ADMINISTERED TO PATIENTS WITH PREËXISTING PARTIAL HEART BLOCK?*

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The orderly transmission of impulses from the auricles to the ventricles may be delayed, may be occasionally blocked, or may be blocked completely. In the latter event, when no impulses pass from auricles to ventricles, auriculoventricular dissociation is said to be present and the term "complete heart block" is applied. Any defect in auriculoventricular conduction short of complete dissociation is called partial heart block.[25]

Mackenzie[17] and Cohn[5,6] demonstrated many years ago that digitalis may produce an effect on auriculoventricular conduction, varying from simple lengthening of the a-c or P–R interval to complete block. In the absence of medication, these conduction defects also are observed not uncommonly in patients with rheumatic or arteriosclerotic heart disease. In treating such patients with preexisting partial heart block, the physician not infrequently is confronted with the difficult decision as to whether digitalis should be prescribed, because of the danger of further interference with the passage of impulses on the one hand, and clear indications for its administration on the other. The proven efficacy of digitalis in patients with normal sinus rhythm[4,15,15b] has caused this problem to assume increasing importance.

So far as we are aware, no suitable body of evidence bearing on this question is available. Various authorities in the past have expressed conflicting opinions. Thus, Robinson, White, Eggleston and Hatcher[22] have stated that "there are certain disorders of the heart which may lead to cardiac failure and which are only exaggerated by the administration of a drug of the digitalis group. In such conditions these drugs are definitely harmful and even dangerous. Cases of partial heart block and a form of cardiac derangement that occurs in diphtheria may be cited as examples.

"In cases of heart block special care and judgment are needed in the use of the digitalis bodies. Depression of conduction is one of the most definite effects that they produce. Therefore, in partial heart block, when further interference with the passage of cardiac

* Read in abstract before the Association of American Physicians, May 2, 1939.

impulses from auricles to ventricles may be injurious, the digitalis bodies are contraindicated."

Likewise, Cushny[8a,b] and Edens[10] have expressed the opinion that digitalis affects especially the conducting system of the heart in which auriculoventricular conduction previously has been impaired because of disease. Lævy and Mackie[14] have stated, "In partial heart block the danger of further depression of auriculoventricular conduction must be considered; complete block may ensue."

Wenckebach[24] declares, "From experiments we may conclude that our therapeutic doses act mainly by their influence on the vagus. In such cases, where conductivity is already impaired, digitalis may do harm, as I predicted as long ago as 1898, and was proved afterwards by many observations.

"The effects of digitalis on heart and circulation being very numerous, we have to reckon with the possibility of a bettered circulation causing a better nutrition of the heart muscle and secondarily improving conductivity and other qualities of the heart. In this way, perhaps, cases in which we saw partial heart block cured by digitalis may be explained."

According to Turnbull,[23] "In cases in which, owing to damage of a-v bundles, the period required for passage of an impulse from auricle to ventricle over the bundle is longer than the normal 0.2 second (a-c interval prolonged), digitalis very frequently further increases this difficulty until some of the impulses fail to pass and a condition of heart block is produced, at first partial, and finally, if the drug be pushed, perhaps complete with blocking of all auricular impulses."

In his excellent treatise on the therapeutic use of digitalis, Robinson[20] states, "The depression of conduction is one of the most definite effects which digitalis produces, as has already been brought out. Therefore, in partial heart block, when further interference with the passage of cardiac impulses from auricles to ventricles is decidedly undesirable, digitalis is contraindicated."

Robinson then discusses cases in which conduction time is lengthened and says that cases are seen occasionally in which this is due to faulty nutrition. In such instances this depression may disappear with an improvement in the state of circulation.

It is the opinion of Luten,[15b] on the other hand, that "its occurrence (lengthening of the P–R interval) does not prohibit the further administration of digitalis, but it necessitates great care, and in most instances, it implies that a favorable response is not to be expected."

Similarly, Eggleston has stated,[11b] "Extensive clinical observations have shown conclusively that while there is an increased tendency for digitalis to enhance a preëxisting depression of conduction or partial block, it is by no means contraindicated in cases of this type. In many such cases it may be administered with satisfactory results

without further prolongation of conduction time or increase in heart block. In others the block, or impaired conduction, seems to be largely secondary to the existence of the heart failure, and when digitalis relieves the failure, the block may disappear or the conduction time may be shortened."

Methods and Materials. Because of these conflicting opinions and the absence of a body of data bearing on this issue, the following study was undertaken. Nineteen patients ranging in age from 15 to 72 years were studied; 13 were males and 6 females. Congestive heart failure was present in almost all. In 14 of the subjects, prolongation of the *P–R* interval was due to coronary sclerosis; in 3 of these there was a varying 2 to 1 and 1 to 1 relationship between auricular and ventricular contractions. The remaining 5 patients had prolonged *P–R* intervals associated with rheumatic heart disease; manifestations of active infection were present in 2.

Digitalis* was administered in doses calculated on the basis of body weight; somewhat less than the full Eggleston dosage was administered.[11a] In the case of edematous patients the actual weight exclusive of the weight of the edema was estimated and the digitalis administered accordingly, as recommended by Eggleston.[11a] The actual weight so estimated in almost every case was in close agreement with the weight found after the loss of edema (Table 1). Digitalization was accomplished within 3 to 9 days. A daily utilization of 0.1 gm. was assumed in calculating the amount of digitalis remaining within the body.[2] Utilization of 0.1 gm. for the first day was excluded since administration was begun usually during the second half of the first day and only negligible amounts could have been utilized. The electrocardiographic tracings following digitalization were taken before the completion of the last day used in the calculation. The errors involved in these calculations tend to give a result too low rather than too high in the calculated amount of digitalis remaining within the body. The dosage per 100 pounds of body weight ranged from 1 to 2.3 gm. and averaged 1.3 gm.

Results. In 6 cases nausea was induced. In the 6 cases in which symptoms of toxicity were precipitated, no significant change in *P–R* interval occurred. In 2 of these patients, changing 2 to 1 and 1 to 1 responses were present before and after digitalization. Of the 19 cases studied, the *P–R* interval did not change in 11; in 3, a lengthening of 0.02 second and in 3 a lengthening of 0.04 second occurred. In 1 patient the *P–R* interval was shortened by 0.04 second and in another the *P–R* interval was shortened by 0.08 second. No alteration in the orderly sequence of auricular and ventricular contractions occurred except that observed in 1 case in which occasional 2 to 1 heart block disappeared and normal 1 to 1 response was established (Table 1).

Discussion. The results demonstrate that digitalis in doses sufficient to induce therapeutic effects may be given to patients with partial heart block without causing interference with the orderly passage of impulses from the auricles to the ventricles. The dos-

* Powdered leaves, U. S. P. Lederle; 0.1 gm. is equivalent to 1 cat unit. All digitalis used was biologically tested by the manufacturer and again biologically tested by us in cats.

TABLE 1.—DIGITALIS DOSAGE AND *P–R* INTERVAL.

Sex. Age. Hosp. No.	Diagnosis.	Symptoms and signs.	Associated conditions.	Weight, edema free.	Amount digitalis administered (days), gm.	Digitalis remaining in body (calculated).		*P–R* interval, sec.		Blood pressure, mm. Hg.		Pulse.		T wave changes.
						Total gm.	Gm./10 lb. body wt.	Before.	After.	Before.	After.	Before.	After.	
M 62 46007	Art. ht. dis., cong. failure	Dyspnea	Coronary occlusion	124	4.2 (14)	2.9*	.23	.24	.24	110/70	120/70	80	45	+
M 51 27319	Hypertension, art. ht. dis., cong. failure	Dyspnea, orthopnea, hepatomegaly, sl. edema and râles	None	120	2.5 (9)	1.7	.14	.22	.22	170/130	140/90	120	80	+
F 72 34239	Hypertension, art. ht. dis. cong. failure	Dyspnea, orthopnea, râles, hepatomegaly, edema, hydrothorax	None	105	1.8 (5)	1.4	.13	.26	.22	160/100	150/100	88	78	+
M 54 19842	Hypertension, art. ht. dis., cong. failure.	Dyspnea, orthopnea, râles, hepatomegaly, edema, hydrothorax	None	130	2.4 (8)	1.7	.13	.24	.24	200/120	180/110	85	65	+
F 50 3172	Hypertension, art. ht. dis., cong. failure	Dyspnea and edema on exertion	Chronic cholecystitis	160	2.1 (4)	1.8	.11	.24	.28	155/75	140/80	70	70	+
M 64 27214	Art. ht. dis., cong. failure	Dyspnea, râles, hydrothorax	Simmonds' cachexia	87	1.3 (4)	1.0	.11	.22	.22	120/80	120/80	85	75	+
M 57 26100	Hypertension, art. ht. dis., cong. failure	Dyspnea, orthopnea, râles, edema	None	110	1.6 (5)	1.2	.11	.24	.28	130/100	120/80	100	80	+
M 70 2201	Hypertension, art. ht. dis., cong. failure	Dyspnea, râles and edema	Diabetes mellitus	170	2.3 (6)	1.8	.11	.24	.24–.28	195/110	200/100	65	65	+

M 67 20821	Art. ht. dis., cong. failure	Dyspnea, orthopnea, râles, hepatomegaly, edema	None	120	1.4 (3)	1.2	.10	.24	.26	130/80	130/80	80	60	+
M 62 45563	Art. ht. dis., cong. failure	Angina pectoris, dyspnea, orthopnea, râles, cardiac asthma	None	142	3.9 (13) ††	?*	?	.28	.28	140/70	140/70	75	65	+
F 60 43762	Art. ht. dis., hypertension, cong. failure	Dyspnea, edema	None	163	1.7 (4) ††	?*	?	.22	.22	145/90	145/90	70	70	?
F 67 7697	Art. ht. dis., cong. failure	Dyspnea on exertion, râles	None	105	1.7 (5)	1.3*	.12	2:1, 1:1	2:1, 1:1	200/80	?	50	50	+
F 52 46261	Art. ht. dis.	Angina pectoris, Stokes-Adams syndrome	None	140	2.0 (4)	1.7*	.12	.24–.28 with 3:2 or 2:1 block	.24–.28 with 3:2 or 2:1 block	110/70	110/70	30–50	30–50	+
M 70 35906	Art. ht. dis., cong. failure	Dyspnea, orthopnea, râles, hydrothorax	Acute coronary occlusion	?	1.9 (3)	1.7	?	.22–.26 with 2:1, 1:1 response	NR .28	170/60	170/60	115	80	+
M 35 46104	Rheum. ht. dis., acute rh. fever, cong. failure	Dyspnea, cyanosis, edema	None	141	2.4 (5) 3.0 (12)	2.0* 1.9*	.14 .13	.36 .32–.34	.44 .34–.36	120/60 120/60	120/60 120/60	80 70	65 65	+ 0
M 55 9065	Rheum. ht. dis., mitral insuff., aortic insuff., cong. failure	Dyspnea, orthopnea, râles, hepatomegaly, edema	None	120	2.1 (7)	1.5	.13	.24	.26	240/70	200/50	60	60	+
M 21 9404	Rheum. ht. dis., aortic insuff., mitral sten. and insuff., cong. failure	Dyspnea, orthopnea, râles	None	100	1.8 (6)	1.3	.13	.32	.24	240/0	250/0	90	85	+
M 15 36197	Rheum. ht. dis., mitral sten., aortic insuff., sl. cong. fail.	Dyspnea at rest	Acute rheumatic fever	100	1.4 (4)	1.1	.11	.28	.28	125/65	?	100	65	+
F 45 17739	Rheum. ht. dis., mitral sten., aortic insuff.	Cardiac asthma, hemoptyses	None	170	2.6 (9)	1.8	.11	.28	.30	120/60	120/70	75	75	+

* Symptoms of toxicity.
†† These 2 patients were partially digitalized on admission, having previously received an undetermined amount of digitalis.

ages employed were those usually employed in treating patients with congestive failure in the hospital; the adequacy of the amounts used was indicated by the therapeutic response; it was not considered relevant to this study to give amounts which would produce toxic manifestations, although in 6 cases nausea occurred without change in the *P–R* interval. We are in agreement with the general opinion[9,14,15b,18a,22,25] that digitalis should not be employed regularly in the largest possible doses on the assumption that the highest level of action that can be induced without intoxication is invariably most effective. Patients often can tolerate much larger doses of digitalis than are necessary to maintain a condition of optimum improvement.[12,28] The studies of dosage by Eggleston have afforded an invaluable guide in regard to digitalis administration, and, as Luten has stated, "represent quantities which in the average should be regarded rather as doses not to be exceeded than as doses to be administered—as top dosage rather than as optimum dosage." It has been shown that the earliest detectable changes in the *T* wave occur when approximately 55% of the total estimated therapeutic dose is within the body and that the more pronounced changes occur with approximately 90% of the full therapeutic dosage.[2] In all instances characteristic pronounced *T*-wave changes induced by digitalis were evident, indicating that sufficient amounts of digitalis had been administered to attain the therapeutic zone of its action.[7,15b] In none of the cases studied did the administration of digitalis precipitate auricular fibrillation.

It is of interest that in several patients shortening of the *P–R* interval was witnessed. This was associated with clinical improvement and presumably is to be attributed to the consequent improved nutrition of cardiac tissue.

It is hardly to be doubted that, if digitalis in greater dosages had been administered, increased lengthening of the *P–R* interval and even complete heart block could have been induced as is the case with even normal subjects.[6,13,16,26] In normal individuals changes in the *T* wave precede changes in auriculoventricular conduction time. The results of the present study indicate that similarly in cardiac patients with partial block the same relationship holds. These considerations are in accord with the experimental findings of Robinson and Wilson[21] who found, after the intravenous administration of digitalis to cats, that inversion of the *T* wave appeared after an average of 24% of the fatal dose, definite prolongation of the *P–R* interval was observed after an average of 52%, ectopic beats after an average of 72% and complete auriculoventricular dissociation was produced by an average of 80% of the lethal dose. Whether excessive doses would produce complete heart block more readily in patients with depressed conduction was not studied, since this question was not considered germane to this investigation and because production of complete dissociation is not without danger.

The production of complete auriculoventricular dissociation, while usually not harmful, may nevertheless result in Adams-Stokes syndrome and therefore is to be avoided.[19a,b]

The results of this study show that while digitalis and organic heart disease each result in interference with auriculoventricular conduction, these factors do not reinforce each other, and their simultaneous presence does not lead to an additive effect when doses such as used in the present study are utilized.

The findings in Case 46007 are of especial interest in that they demonstrate the difficulty of interpreting the relation of changes in *P–R* interval to the administration of digitalis in patients experiencing an exacerbation of acute rheumatic fever (Table 2). In this instance the administration of digitalis during an exacerbation of rheumatic fever was apparently followed by a marked increase in the length of the *P–R* interval from 0.36 to 0.44 second. However, subsequent digitalization to the point of nausea after the subsidence of the exacerbation of rheumatic fever was associated with no change in *P–R* interval, the latter remaining at approximately 0.34. It is clear, therefore, that the increase in *P–R* interval associated with the first course of digitalis was due not to the drug but rather to the flare-up of rheumatic fever.

TABLE 2.—DIGITALIS DOSAGE AND *P–R* INTERVAL IN CASE 46007.

Date.	Digitalis dose, gm.	*P–R* interval, sec.	Remarks.
Mar. 7		.30	
20		.36	Acute rheumatic fever.
23		.36	
24	.8		
25	.6		
26	.5		
27	.4	.44	
28	.1	.44	Nausea.
29		.42	
30		.38	
31		.44	Subsidence of rh. fever.
April 1		.32	
3		.34	
5	.3	.34	
6 (A.M.)	.3	.36	
6 (P.M.)		.34	Nausea.
7		.36	

As Luten[15b] has pointed out, the failure of an auricular impulse to elicit a ventricular response is explainable on either of two suppositions: (*a*) either the impulse fails to reach the ventricle, or (*b*) reaching it, finds the ventricle unresponsive. The lengthened *P–R* interval associated with active rheumatic carditis has been shown by Bruenn[3] to be largely vagal in origin; that associated with arteriosclerotic heart disease may be similar or due to structural changes in the auriculoventricular conduction system.[1]

In both instances the effect is on the conduction system either

directly because of a pathologic lesion or indirectly through the vagus nerves. However, there is much evidence, clinical and experimental, to show that heart block due to digitalis in therapeutic dosage is referable, in part at least, to the action of the drug upon the musculature of the ventricle, rendering it less excitable to auricular stimuli.[15b] The results reported in this study would seem to be in accord with this concept.

Finally, attention should be drawn to the fact that, although digitalis in doses of 0.1 to 0.23 gm. per 10 pounds of body weight did not greatly increase preëxisting heart block in any case of this series, it is impossible to preclude the possibility that occasional or rare instances may be encountered in which this may occur, particularly if dosages approaching toxic amounts are employed. Certain observers have stated that complete heart block has been observed to occur when only small or moderate doses were given to patients with partial heart block.[27] Caution and careful observation, therefore, should be exercised, particularly if larger doses than those employed by us are utilized.

Summary and Conclusions. In treating patients with preëxisting partial heart block, the physician is not infrequently confronted with the difficult decision as to whether digitalis should be prescribed, because of the danger of further interference with the passage of impulses on the one hand, and clear indications for its administration on the other. So far as we are aware, no suitable body of evidence bearing on this question is available.

Nineteen patients ranging in age from 15 to 72 years were studied. Congestive heart failure was present in almost all subjects. In 3, a varying 2 to 1 and 1 to 1 relationship between auricular and ventricular contractions existed. In most of the patients prolongation of the *P–R* interval was due to coronary sclerosis; in the others, rheumatic heart disease was present.

A standardized preparation of digitalis was administered in doses calculated on the basis of body weight; in accord with general practice, somewhat less than the full Eggleston dosage was administered.

The results demonstrate that digitalis in doses sufficient to induce therapeutic effects may be given to patients with partial heart block without causing interference with the orderly passage of impulses from the auricles to the ventricles. The dosages employed were those usually employed in treating patients with congestive failure in the hospital; the adequacy of the amounts used was indicated by the therapeutic response; it was not considered germane to this study to give amounts which would produce toxic manifestations, although in 6 cases nausea occurred without change in the *P–R* interval.

The results of this study show that while digitalis and organic heart disease each result in interference with auriculoventricular conduction, these factors do not reinforce each other and their simul-

taneous presence does not lead to an additive effect when doses in therapeutic amounts such as were used in the present study are utilized. The presence of partial heart block does not constitute a contraindication to the use of digitalis.

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EXPERIMENTAL ARTHRITIS IN RABBITS PRODUCED WITH STREPTOCOCCI AND OTHER ORGANISMS.*†

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Although it has been known for over 50 years that arthritis can be readily produced in rabbits with various strains of streptococci, there have been few experimental studies on the pathogenesis and course of infectious arthritis.

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† A preliminary report of these studies was presented at the meeting of the Association of American Physicians in Atlantic City, May 5, 1938, and published in the Transactions.

There are many reports on attempts to produce acute or chronic arthritis in rabbits with various strains of streptococci. One group of experiments has been reported by those who have tried to reproduce the pathologic picture of acute rheumatic fever in rabbits with organisms obtained from the blood and joints of patients with that disease.[2,10,14,16,18–21]

Another group, interested in chronic arthritis, has produced lesions in the joints of rabbits with various streptococci obtained from cultures of the blood, throat or teeth of patients with chronic infectious arthritis. They concluded that because these organisms produced arthritis so readily in rabbits, they were probably of etiologic significance in the disease.[3,8,9,12]

Cole,[4] Davis[6] and McMeans,[15] however, showed that the source of these so-called arthrotropic streptococci was of little importance so far as the production of arthritis in rabbits is concerned. These authors demonstrated that streptococci obtained from patients with peritonitis, puerperal septicemia, empyema, appendicitis, scarlet fever, endocarditis, and nephritis produced arthritis in rabbits as readily as did streptococci obtained from patients with arthritis.

Jackson[11] made a careful histologic study of the joints of rabbits in which arthritis had been produced by intravenous injections of hemolytic streptococci obtained from the tonsils of patients during the epidemic of sore throat in Chicago in 1911 and 1912. The doses of bacteria injected were so large that in many instances the joints were completely destroyed. Hadjopoulos and Burbank[9] made a histologic study of the joints in experimental arthritis in rabbits. They have attributed the chronic character of the lesion produced to the fact that the streptococci used in their experiments were avirulent and obtained from cases of chronic arthritis. No control experiments were reported. Jarløv and Brinch[12] have also recently reported an experimental study of streptococcus arthritis in rabbits. They made a detailed study of the nature of the joint lesions and have attributed much importance to the fact that the organisms used came from patients with arthritis. However, they have not used a sufficient number of organisms from other sources as controls.

Our chief object in undertaking the present investigation was to study the pathogenesis of streptococcus arthritis in rabbits. However, since little attention has been given to any organism other than the streptococcus so far as the production of experimental arthritis is concerned, it seemed advisable for us to include several other types of bacteria in such a study.

Method. Healthy albino rabbits that weighed from 1800 to 2400 gm. have been used throughout the experiments. The majority of the animals were males.

Two cultures of Group A hemolytic streptococci (Strains AB 13 and NY 5) and one of *Strep. viridans* were used. Strain AB 13 was obtained from the

blood of a patient with rheumatoid arthritis,[17] and Strain NY 5 was isolated from a case of scarlet fever by Dochez. The strain of *Strep. viridans* was freshly isolated from the blood of a patient with subacute bacterial endocarditis.

To determine the arthritis-producing capacity of several other bacteria, we have used the following for intravenous injection: *Staph. aureus, Pneum. Types I and XIV, B. paratyphosus* A, *B. typhosus, B. coli communior, B. dysenteriæ* (Flexner), *Proteus X 19, Br. abortus* and *Br. melitensis.*

Most of the rabbits were given single intravenous injections of an 18-hour broth culture; some received more than one injection. The dose (Table 1) was varied according to the virulence of the organism.

They were bled from the ear vein before injection, after that at 2, 4 and 8 weeks, and then at monthly intervals to determine the sedimentation rate and the agglutinin titre of the sera. The fall of the red blood cells was recorded in millimeters per hour. In order to determine the sensitivity of the animals to streptococci, skin tests were done on a large number of animals with an homologous 48-hour broth filtrate. Frequent Roentgen-ray examinations were made of the involved joints.

A considerable number of the affected joints were aspirated and the synovial fluid examined and cultured. Blood cultures were taken frequently during life and routinely at autopsy. Complete autopsies were performed in every instance, and the joints opened and examined. The synovial fluid, as well as the synovial tissue, of the affected joints was usually cultured. Smears of the exudate were made in order to study the cytology and to determine whether organisms were present.

TABLE 1.—INCIDENCE OF ARTHRITIS PRODUCED IN RABBITS WITH A SINGLE INTRAVENOUS INJECTION OF DIFFERENT STRAINS OF STREPTOCOCCI.

Organism.	Dose in cc.	No. of rabbits.	Rabbits with arthritis.	
			Number.	Per cent.
Strep. hemolyticus	4.0	5	5	100.0
Strain AB 13	2.0	25	17	68.0
	1.0	21	7	33.3
	0.1	25	6	24.0
Strep. hemolyticus	1.0	6	5	83.3
Strain NY 5	0.5	20	13	65.0
Strep. viridans	2.0	22	11	50.0
	1.0	2	1	50.0

Incidence of Arthritis in Relation to the Dose and the Number of Intravenous Injections. A group of 76 rabbits received single intravenous injections of broth culture of hemolytic streptococcus (Strain AB 13). The dose varied from 0.1 to 4 cc. (Table 1). Of 13 additional rabbits that received less than 0.1 cc., none developed arthritis. It is obvious that the larger doses produced arthritis more readily than did the smaller. An occasional animal died from 4 cc. of culture, whereas smaller amounts were never fatal. From this series of animals it was evident that a single injection of 2 cc. of broth culture was the most suitable dose with which to produce arthritis in a fairly high percentage of animals. It is of interest that one-half of this dose (1 cc.) produced arthritis in only 33% of the injected rabbits, whereas the larger dose (2 cc.) produced arthritis in 68%. Another group of 39 rabbits received 3 injections of 0.1, 1 and 2 cc.

respectively of the same strain of streptococcus at 10-day intervals, and of these 36 (92.3%) developed arthritis.

Eighteen of 26 rabbits developed arthritis following an intravenous injection of *Strep. hemolyticus* (Strain NY 5) in amounts of 0.5 or 1 cc. It was necessary to use somewhat smaller doses of this organism because, when more than 1 cc. of culture was injected, the animal usually died. Although an occasional animal died after 0.5 cc. of culture, this was a satisfactory dose for the production of arthritis.

Twelve of 24 rabbits that received 1 or 2 cc. of *Strep. viridans* culture intravenously, and 2 of 4 rabbits that received more than one injection, developed arthritis.

When one compares the incidence (Table 1) of arthritis produced by the 3 strains of streptococci with doses of about the same size, it is evident that Strain NY 5 produced arthritis somewhat more frequently in our series than did Strain AB 13. Seventeen (68%) of 25 rabbits injected with 2 cc. of Strain AB 13 developed arthritis, whereas 5 (83.3%) of 6 injected with 1 cc. and 13 (65%) of 20 injected with 0.5 cc. of NY 5 developed arthritis. *Strep. viridans* produced arthritis in 11 (50%) of 22 rabbits that received 2 cc. of culture intravenously.

TABLE 2.—PRODUCTION OF ARTHRITIS WITH A SINGLE INTRAVENOUS INJECTION OF VARIOUS ORGANISMS.

Organism.	Dose in cc.	No. of rabbits.	Rabbits with arthritis.	
			Number.	Per cent.
Staph. aureus	0.05–2.0	17	13	76.5
Pneumococcus	1.0 –2.0	11	4	36.4
B. paratyphosus A	1.0 –2.0	6	1	16.7
B. typhosus	1.0 –2.0	6	0	0
B. coli communior	0.5 –2.0	7	0	0
B. dysenteriæ Flexner	0.01–0.1	6	0	0
Proteus X 19	0.5 –2.0	6	0	0
Br. abortus	2.0	6	0	0
Br. melitensis	2.0	6	0	0

In order to determine the incidence of arthritis produced with organisms other than streptococci, 71 animals (Table 2) were injected. Of 17 that received *Staph. aureus*, 13 (76.5%) developed arthritis. Nineteen additional rabbits died within 3 days after the intravenous injection. Four of 11 rabbits injected with *Pneumococcus* and 1 of 6 with *B. paratyphosus A* developed arthritis, whereas none of the 37 rabbits that received injections of *B. typhosus*, *B. coli communior*, *B. dysenteriæ* (Flexner), *Proteus X 19*, *Br. abortus* or *Br. melitensis*, did so.

Incidence of Arthritis in Relation to Sex. The animals were selected for these experiments without regard to sex, although the majority were males. When we analyzed the development of arthritis in relation to sex, the results indicated that arthritis occurred more frequently in females than in males. Only those that received single comparable doses of the same organism were included.

Thirty (40.5%) of 74 male rabbits developed arthritis as contrasted with 21 (75%) of 28 female rabbits. Many uncontrolled factors other than sex may have been responsible for this difference.

Observations on the Course of Arthritis. The animals were observed daily for 10 days and thereafter at frequent intervals to determine whether arthritis developed. When a joint became involved, the rabbit favored the affected extremity by holding it off the floor and by hopping or limping. Arthritis usually developed from the 3rd to the 7th day, although it was occasionally observed within 48 hours or as late as 12 days after injection. One could readily localize the affected joint by palpation. There was usually swelling, increase in surface temperature and, occasionally, fluctuation. In many instances the swelling rapidly subsided, and the animal began to use the joint again within 2 to 3 weeks. Although arthritis was frequently observed in several joints in the same animal, it did not develop in additional joints after the first 12 days. If the swelling did not subside within a short time, the joints frequently remained involved for several months and in this case there was often proliferation of bone, increase of fibrous connective tissue and partial ankylosis. The progress of the alterations in the bony structures of the joint was followed by means of Roentgen-ray photographs. The protocol of 1 rabbit in which these chronic changes occurred may be of interest.

Rabbit 119: Two cubic centimeters of an 18-hour broth culture of hemolytic streptococci (Strain AB 13) were injected intravenously on December 31, 1936. Eleven days later the animal held the right leg flexed; there was swelling of the right knee joint and pain on movement. The joint was aspirated, and a large number of neutrophils and a few cocci were seen in a smear of the synovial fluid. Hemolytic streptococci were grown in culture. The knee joint was aspirated 12 days later; there were fewer neutrophils and a considerable number of monocytes in the synovial fluid, a culture of which was sterile. After 6 months (Fig. 1) the joint was still swollen, tender and flexed, and there was crepitus on movement. Except for a slight decrease in swelling, there was no change for 23 months. The serum agglutinins against Strain AB 13 increased during the first 2 months up to 1:1280, but were not present after 4 months. The sedimentation rate increased to 45 millimeters per hour during the first 2 months and returned to normal after 4 months. At autopsy the right knee joint revealed no excess of synovial fluid; the synovial membrane, however, was thicker than normal. The cartilage had lost its normal lustre, and there was considerable degeneration of both bone and cartilage over the lower end of the femur. The cruciate ligaments were thick and shortened, and the joint could not be fully extended. Cultures of synovial tissue were sterile. Microscopically, the joint capsule and synovia showed an increase of fibrous connective tissue but no cellular infiltration.

One group of 22 rabbits that developed arthritis was permitted to live until gross or Roentgen-ray evidence of arthritis had disappeared, or were killed at intervals for bacteriologic and histologic study. The average duration of arthritis in these rabbits was about

15 weeks. One animal that received a single intravenous injection of hemolytic streptococci 2 years previously is still living and has a chronic arthritis of the right elbow associated with partial ankylosis.

The distribution of the joints in which arthritis developed in 198 rabbits was as follows: 130 shoulders, 89 knees, 42 elbows, 39 wrists, 12 hips, 8 interphalangeals, and 6 ankles. In a few animals more than one of the contralateral joints were involved.

Bacteriologic Studies of Blood and Joints. Blood cultures were taken on many animals for several days after injection. The organisms rapidly disappeared from the blood and were seldom recovered in cultures after about the 5th or 6th day. Routine cultures of the heart blood and in several instances, of the spleen, were made at autopsy. These were always sterile in animals that lived for 2 or more weeks following injection.

TABLE 3.—RESULTS OF CULTURES OF SYNOVIAL FLUID AND TISSUE.

Weeks after injection.	Synovial fluid (aspirated)		Synovial fluid (postmortem)		Synovial tissue (postmortem)	
	Growth.	No growth.	Growth.	No growth.	Growth.	No growth.
1	3	3	7	2		
2	4	11	6	7	4	2
3	1	5	6	11	7	11
4–6			5	8	6	8
6–8	0	1	1	3	0	2
8–10	1	0	0	13	2	14
10–12			0	2	0	2
12–60			0	7	0	12
Totals	9	20	25	53	19	51

Affected joints were aspirated (Table 3) at intervals to obtain synovial fluid for culture and cytologic study. During the first 3 weeks of arthritis the exudate within the joint cavity was opaque and viscid, but although it contained many neutrophils was seldom purulent. It was purulent, however, in animals that had received large doses or repeated intravenous injections of hemolytic streptococci. Streptococci were readily grown from aspirated synovial fluid during the first week, and after that with increasing difficulty. Aspirations were not done repeatedly, nor on a greater number of animals, because of the trauma caused by this procedure. Cultures of the synovial fluid and tissue at autopsy were usually sterile after the 6th week (Table 3), although organisms were recovered in a few instances 8 weeks after injection. The synovial fluid gradually became clear but was present in excess for several months.

To determine how long organisms would remain viable in the joint 4 cc. of a broth culture of hemolytic streptococci (Strain AB 13) concentrated to a volume of 0.1 cc., were injected into the right knee joint of 12 rabbits (Table 4). Seven rabbits were given single injections, and 5 received multiple injections. The animals were killed at intervals of from 9 to 81 days. Of those that

FIG. 1.—Swelling of the right knee joint of Rabbit 119, 6 months following an intravenous injection of 2 cc. of broth culture of hemolytic streptococcus (Strain AB 13).

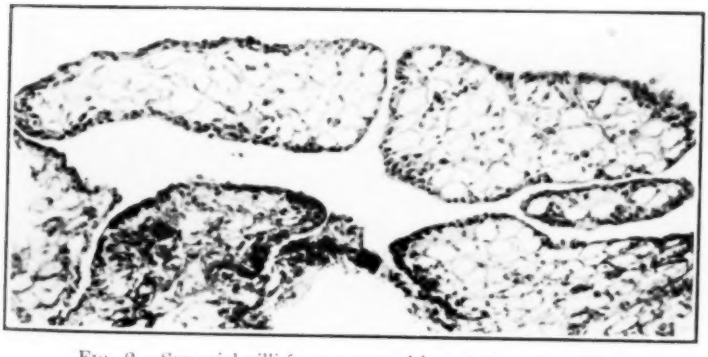

FIG. 2.—Synovial villi from a normal knee joint. (× 170.)

FIG. 3.—Early inflammation in a synovial villus of a knee joint 48 hours after an intravenous injection of 1 cc. of broth culture of hemolytic streptococci. (× 170.)

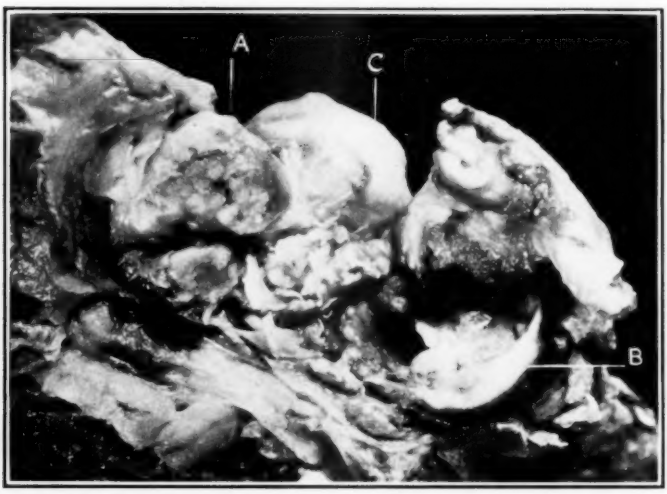

FIG. 4.—Arthritis of shoulder joint of Rabbit 124, 3 months after an intravenous injection of 0.1 cc. of a broth culture of hemolytic streptococcus (Strain AB 13). The joint has been opened to expose the head of the humerus (*A*) and the glenoid fossa (*B*) which are still attached to the joint capsule (*C*). There is considerable degeneration of the articular cartilage over the head of the humerus. The synovia is thicker than normal and covered with numerous readily visible synovial villi.

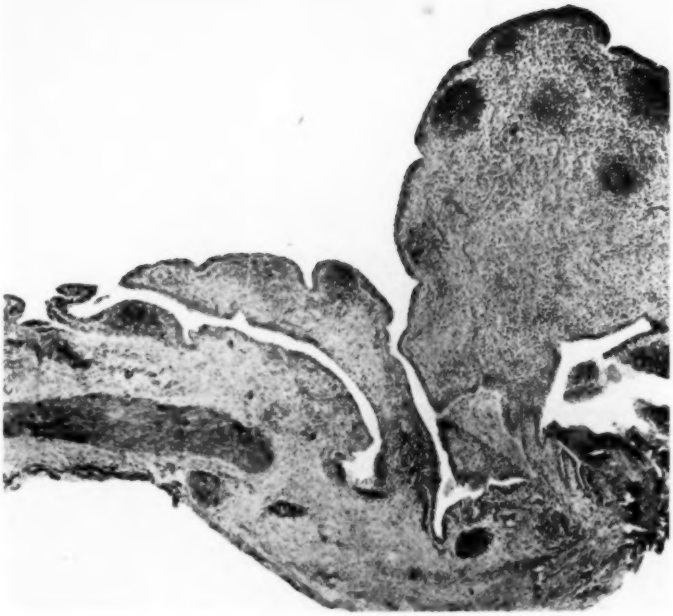

FIG. 5.—Synovial tissue from the shoulder joint shown in Figure 4. Note the prominent villi and focal accumulations of lymphocytes. (× 50.)

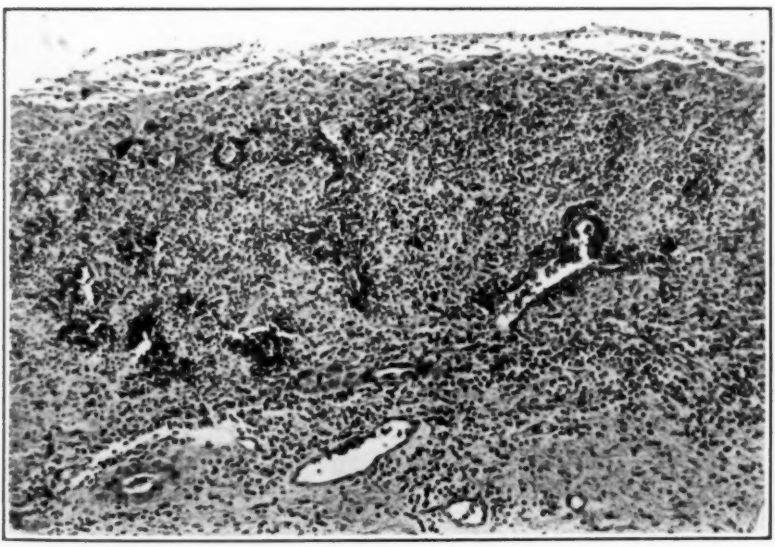

FIG. 6.—Showing perivascular collections of lymphocytes in a section of synovia from the shoulder joint of Rabbit 654, 3 weeks after an intravenous injection of 2 cc. of broth culture of hemolytic streptococci. (× 170.)

FIG. 7.—From the same section shown in Figure 6. Note the dense collection of lymphocytes in the subsynovial tissue. (× 170.)

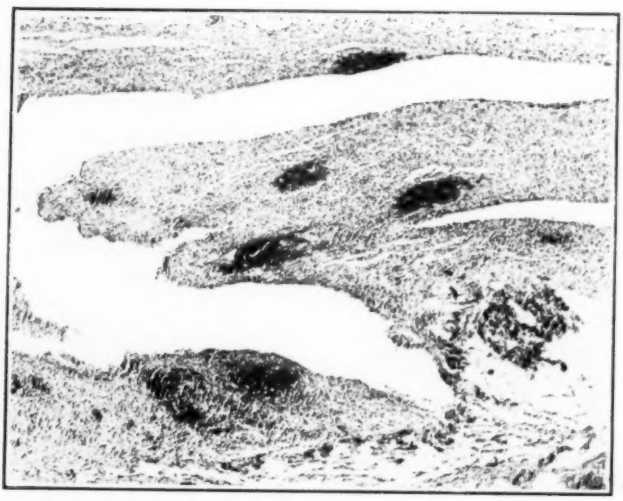

FIG. 8.—Section of synovial tissue from the left knee joint of a rabbit 43 days after an intravenous injection of 2 cc. of a broth culture of pneumococcus Type XIV. Note the focal accumulation of lymphocytes. (× 68.)

received single injections, streptococci were not recovered from the synovial fluid or tissue after 21 days, and in only one of the 5 rabbits that had received multiple injections were organisms recovered from the joint as late as 30 days after the last injection.

TABLE 4.—RESULTS OF CULTURE OF JOINTS AFTER INTRA-ARTICULAR INJECTIONS OF HEMOLYTIC STREPTOCOCCUS (STRAIN AB 13).

Rabbit number.	Dose in cc.	Days after injection.	Material cultured.	
			Synovial fluid.	Synovial tissue.
1	4.0	9	Growth	Growth
2	4.0	21	Growth	Growth
3	4.0	35	No growth	No growth
4	4.0	40	No growth	No growth
5	4.0	51	No growth	No growth
6	4.0	63	No growth	No growth
7	4.0	81	No growth	No growth
8	4.0*	30	Growth	Growth
9	4.0*	30	No growth	No growth
10	4.0*	30	No growth	No growth
11	4.0*	30	No growth	No growth
12	4.0*	30	No growth	No growth

* 3 injections.

Serologic Tests. The sedimentation rate and agglutination titre were determined on all animals injected with hemolytic streptococci at 2, 4 and 8 weeks and thereafter at monthly intervals as long as the animals survived. Skin tests were done on 48 rabbits in order to determine sensitivity to streptococcus filtrate. The results, recorded in Table 5, are concerned only with those animals on which several observations were made.

TABLE 5.—THE SEDIMENTATION RATE, AGGLUTINATION TITRE AND SKIN TEST IN RABBITS THAT RECEIVED INTRAVENOUS INJECTIONS OF HEMOLYTIC STREPTOCOCCI.

	Sedimentation rate.			Agglutination titre.			Skin test.		
	No. of rabbits.	No. increased.	% increased.	No. of rabbits.	No. positive.	% positive.	No. of rabbits.	No. positive.	% positive.
With arthritis	35	34	97.1	55	49	89.1	43	18	41.8
With no arthritis	12	10	83.3	13	5	38.4	5	2	40.0

The sedimentation rate usually increased during the first month and returned to normal within 2 months. It was increased in 34 (97.1%) of 35 rabbits that developed arthritis and in 10 (83.3%) of 12 injected rabbits in which no arthritis was demonstrated.

The agglutination titre was determined on the sera of many animals before injection, and in no instance did they agglutinate cultures of hemolytic streptococci. Agglutinins were present within 2 weeks after inoculation, reached a maximum after 1 month and slowly disappeared unless the animal were reinfected. The titre usually varied directly with the dosage. Agglutinins were demonstrated in 49 (89.1%) of 55 injected rabbits that developed arthritis and in 5 (38.4%) of 13 in which there was no arthritis.

Of the 48 animals on which skin tests were made with a homologous streptococcus filtrate, sensitivity was demonstrated in 18 (41.8%) of 43 with arthritis and in 2 (40.0%) of 5 that did not develop arthritis.

TABLE 6.—INCIDENCE OF ARTHRITIS PRODUCED BY THE INJECTION OF HEMOLYTIC STREPTOCOCCI (STRAIN AB 13) INTO VARIOUS SITES.

Site of injection.	No. of rabbits.	Rabbits with arthritis.	
		Number.	%
Gum	16	7	43.8
Maxillary sinus	17	4	23.5
Knee joint	16	2*	12.5
Kidney pelvis	16	1	
Eye	13	1	
Pleural cavity	11	1	
Prostate	7	1	
Uterus	7	1	
Testis	5	0	0
Fallopian tubes	5	0	0
Skin	10	0	0
Peritoneal cavity	10	0	0
Gall bladder	6	0	0
Nose	4	0	0
Oral cavity	4	0	0
Total	147	18	12.2

* Arthritis observed in non-injected joints.

The Production of Arthritis by the Injection of Hemolytic Streptococci (Strain AB 13) into Various Sites. The following experiment was undertaken to study the production of arthritis in rabbits injected by other than the intravenous route, and the relationship of the invasion of the blood stream to the subsequent development of arthritis. An attempt was made to establish foci at various sites in rabbits by means of single or multiple injections of bacteria (Table 6). The usual dose was 4 cc. of an 18-hour broth culture concentrated to a volume of about 0.1 cc. The following methods were used:

1. Suspensions of hemolytic streptococci were injected into the following: the gum, maxillary sinus, prostate, testis, anterior chamber of the eye, pleural and peritoneal cavities, joint and skin.
2. Segments of the uterus or Fallopian tubes were isolated by ligature and injected.
3. The renal pelvis was injected after ligation of the ureter.
4. The gall bladder was injected after ligation of the cystic duct.
5. The animals in one group were fed large amounts of hemolytic streptococcus cultures over a considerable period of time.
6. Pledgets of cotton were soaked with streptococci and packed firmly into the nares where they remained for several weeks.

The injected organisms usually produced a localized abscess at the site of injection. However, it was difficult to establish an infected focus from which streptococci could be recovered longer than from 2 to 3 weeks after injection. By means of the sedimentation rate

and agglutinin titre of the blood, we were able to obtain some evidence as to how long the focus of infection persisted. The focus was cultured at autopsy and in most instances was sterile.

We were, however, successful in establishing a focus in the eye with small doses of streptococci and were able to recover organisms from it 30 days after a single intraocular injection. Arthritis developed in only 1 of 13 of these rabbits, and it appeared within 6 days after injection.

Arthritis was noted in 18 (12.2%) of 147 rabbits (Table 6) within a few days after infection. It was observed in 7 (43.8%) of 16 rabbits injected into the gums and in 4 (23.5%) of 17 injected into the maxillary sinuses. Arthritis also developed in a few of the animals that had received injections of streptococci into the knee joint, kidney pelvis, eye, pleural cavity, prostate or uterus.

To determine to what extent organisms invaded the circulation, blood cultures were made on most of the animals at intervals of 1, 6, 24 and 48 hours after injection. In the group of rabbits injected into the gums (Table 7) arthritis developed in all 6 of the animals with positive blood cultures and in only 1 of 10 with sterile cultures. Of 102 rabbits, 12 (26.7%) of 45 with positive blood cultures developed arthritis in contrast to only 4 (7.0%) of 57 with negative blood cultures. When animals were injected repeatedly into the same site, the blood was cultured following each injection. Streptococci were frequently recovered after the first injection but were seldom found after subsequent injections.

TABLE 7.—EXPERIMENTAL ARTHRITIS IN RELATION TO INVASION OF THE BLOOD STREAM AFTER INJECTION OF HEMOLYTIC STREPTOCOCCI INTO THE GUMS.

Rabbit number.	Colonies per cc. of blood.				Arthritis.
	1 hr.	6 hrs.	24 hrs.	48 hrs.	
1 . . .	1	1	110	5	+
2 . . .	4	14	22	1	+
3 . . .	8	4	15	3	+
4 . . .	39	22	115	320	+
5 . . .	12	3	3	2	+
6 . . .	40	10	22	2	+

Pathologic Anatomy. Although there are adequate anatomic descriptions of the synovial villi of joints, they have been almost entirely overlooked in previous reports of experimental arthritis. It soon became evident that the villi must be considered in any study on pathogenesis, and the knee was found to be most satisfactory for such a study.

When the joint of a rabbit is opened, the synovial lining is normally smooth and glistening. If it is submerged in saline and examined with a dissecting microscope, one sees minute floating villi which are somewhat larger at the free ends than at the point of attachment and are either single or branched. A fine network of blood vessels is readily seen through the membrane. In addition

to villi there are also small folds of synovia and tissue. Both the villi and synovial folds are most numerous at the junction of synovia and cartilage and also at the site of ligamentous attachments. Villi are numerous over the infra-patellar pad of fat and at the site of the hinge joint in the patella. When one prepares sections of normal rabbit joints for histologic examination, folds of synovia are frequently seen, but intact villi are rare. Their site is usually represented by a loss of continuity in the synovial membrane. If, however, at autopsy, fixative is injected into the joint with a fine needle, using care not to distend the joint capsule, the villi are fixed in their normal relationship so that they are readily seen in sections from joints prepared in this manner (Fig. 2).

When streptococci lodge in the joints of rabbits after intravenous injection, they cause an extensive accumulation of neutrophils in the synovial fluid which increases in amount and becomes viscid and opaque. Streptococci are present in smears and are readily cultured. The inflammatory exudate usually appears first in synovial villi (Fig. 3) which become large and edematous with an infiltration of neutrophils throughout the synovia and subsynovial tissue. Within 48 hours monocytes and lymphocytes are present in fairly large numbers. The subsequent findings depend upon whether the arthritis heals or persists as a chronic infection.

When arthritis persists for 3 or more weeks, the acute inflammation in the synovial membrane subsides, and the synovial fluid contains fewer cells. In some instances after 12 weeks the villi were prominent and visible with the naked eye (Fig. 4). A photomicrograph of these villi is shown in Figure 5.

After from 4 to 6 weeks, mononuclear leukocytes, lymphocytes and plasma cells predominate, although neutrophils are still present. Considerable numbers of fibroblasts are also seen throughout the subsynovial tissue. Lymphocytes accumulate beneath the synovial membrane as well as about small capillaries (Fig. 6) in the granulation tissue. As they increase in number, they form dense focal collections (Fig. 7) which in some instances resemble lymph follicles (Fig. 5), although no definite germinal centers are observed. Similar collections of lymphocytes, frequently associated with fibrosis of marrow, are seen in the epiphyses adjacent to the affected joints. The blood vessel walls are thicker than normal, and there is proliferation of the endothelium with narrowing of the lumen. In some sections there is a pannus of fibrous connective tissue over the cartilage often associated with degeneration of both hyaline cartilage and bone. Deposits of amyloid were present in the liver, kidney and spleen of a few rabbits with chronic arthritis that lived for several months.

Staphylococci produced extensive suppuration in the joints, but when the acute inflammation had subsided, there were no conspicu-

ous differences from the streptococcus arthritis previously described. That produced with pneumococci (Fig. 8) was also very similar to streptococcus arthritis. However, since we had comparatively few rabbits infected with staphylococci or pneumococci, we were unable to make any detailed study of the pathologic lesions produced in the joints with these organisms.

Discussion. Although various strains of streptococci readily produce arthritis in rabbits, it is evident that other organisms, namely staphylococci and pneumococci, can do so almost as well, but probably somewhat less consistently.

Of the bacteria employed in these investigations, a hemolytic streptococcus (Strain AB 13) obtained from a patient with rheumatoid arthritis,[17] proved to be a satisfactory organism with which to produce arthritis in rabbits although it had been carried on laboratory media for about nine years. The two other strains of streptococci that produced arthritis in a high percentage of instances were not obtained from patients with arthritis. These findings are in accord with those of Cole,[4] Davis[6] and McMeans[15] who state that the source of the streptococcus has little to do with the property of elective localization.

Our experiments on the pathogenesis of infections in joints indicate that the anatomic structure of the synovial villi may be as important as the capacity of various microörganisms to localize in the synovia.

Since the hemolytic streptococcus, if not the actual etiologic agent, may be connected in some manner with rheumatoid arthritis, it is necessary to consider whether the experimental arthritis is in any way comparable to the human disease. Experimental infectious arthritis occurred more frequently in female than in male rabbits. The sedimentation rate was increased but rapidly returned to normal. Agglutinins for hemolytic streptococci were demonstrated in a fairly high percentage of animals but did not persist for any length of time. The alterations in sedimentation rate and agglutinin titre were observed, however, in rabbits that did not develop arthritis. The experimental disease was never migratory; furthermore, the involved joints were not those usually affected in rheumatoid arthritis. The latter point is not entirely comparable, because of differences in function of similar joints in rabbit and man.

When the acute inflammation in the infected joint subsides and the arthritis has become chronic, the pathologic picture is very similar to that described as typical of rheumatoid arthritis in man.[7,1] The question then arises whether the histopathology of the joints in rheumatoid arthritis is sufficiently characteristic to be considered specific. The more material one examines from patients with various types of joint disease, the more one is impressed by the fact that the

pathologic picture of rheumatoid arthritis may not be specific.[5] A similar lesion can be produced in the synovial tissue of animals by a variety of agents. The character of the lesion in many instances is probably modified as much by the manner of the response of the synovia to an irritant as by any particular property of that irritant. This point has been well illustrated by Jordan.[13] He shows a photomicrograph of an inflammatory process in the synovial tissue of rabbits which was produced by turpentine and which is indistinguishable from the experimental streptococcal arthritis we have described.

Summary and Conclusions. 1. When small doses of various strains of streptococci were injected intravenously into rabbits, an acute arthritis was produced in several joints and in many instances became chronic. Experimental arthritis was successfully produced with both *Strep. hemolyticus* and *Strep. viridans*. The type of disease from which the streptococcus was isolated bore no relationship to its capacity to produce arthritis. Repeated injections considerably increased the incidence of arthritis.

2. Of several other species of bacteria injected, only *Staph. aureus*, *Pneumococcus* and *B. Paratyphosus A* produced arthritis. The pathologic picture was very similar to that produced with streptococci.

3. Arthritis was observed more frequently in female than in male rabbits.

4. Arthritis usually appeared within a few days after intravenous injection during the stage of bacteremia and seldom developed after the streptococci had disappeared from the circulation.

5. Streptococci were repeatedly grown from synovial fluid during the first 2 or 3 weeks after injection and occasionally from the synovial fluid or tissue as late as 10 weeks.

6. The sedimentation rate was increased in 97.1% and the agglutinin titre elevated in 89.1% of the animals that developed arthritis. The skin test with streptococcus filtrate was positive in only 41.8%. Similar results were obtained in rabbits that did not develop arthritis.

7. Arthritis was produced in 18 (12.2%) of 147 rabbits injected by other than the intravenous route. It occurred most frequently following injection into the gums or sinuses. However, the development of arthritis in these animals was related to the degree of bacterial invasion of the blood stream during the first 48 hours after injection rather than to a later dissemination of bacteria from an infected focus.

8. The pathologic lesion of the synovia in chronic streptococcus arthritis in rabbits is very similar to that commonly associated with rheumatoid arthritis in man. However, in our opinion the specificity of the synovial lesions in rheumatoid arthritis has not yet been established.

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CLINICAL EXPERIENCE WITH GLOBIN INSULIN.

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In the non-diabetic, insulin activity fluctuates with the amount of glucose that enters the blood stream; that is, it is greater during the postprandial periods. It does not seem probable that a depot preparation can ever be sufficiently controlled to fulfill this requirement. However, a product that exerts its maximum activity during the day, when food is being assimilated, is preferable to one that releases the hormone continuously at a more or less even rate during the entire 24 hours. For, when the latter is injected daily, it may produce a hypoglycemia which becomes most disturbing during the early morning hours, a time when insulin shock is easily overlooked. Protamine zinc insulin, whether administered in the evening or in the morning, is apt to have this effect. In severe cases of diabetes it is usually necessary to supplement protamine zinc insulin with standard insulin.

Other disadvantages[1] observed in the use of protamine zinc insulin are local reactions at the site of injection, possibly allergic in nature, and the inaccuracy and inconvenience of injecting a suspension.

It is apparent that further search for an insulin compound with more desirable properties is warranted.

Of the various preparations tested on rabbits and dogs,[2] it was found that a combination of globin insulin and zinc seemed to be

most promising. Its action lasts more than twice as long as that of standard insulin, yet it develops its full activity not much later (see curves). This is in marked contrast to protamine zinc insulin, which in rabbits reaches its full activity only after 10 hours, yet the effect is prolonged over 24 hours when only 0.5 unit per kg. (an amount comparable to 25 to 35 units for man) is administered.

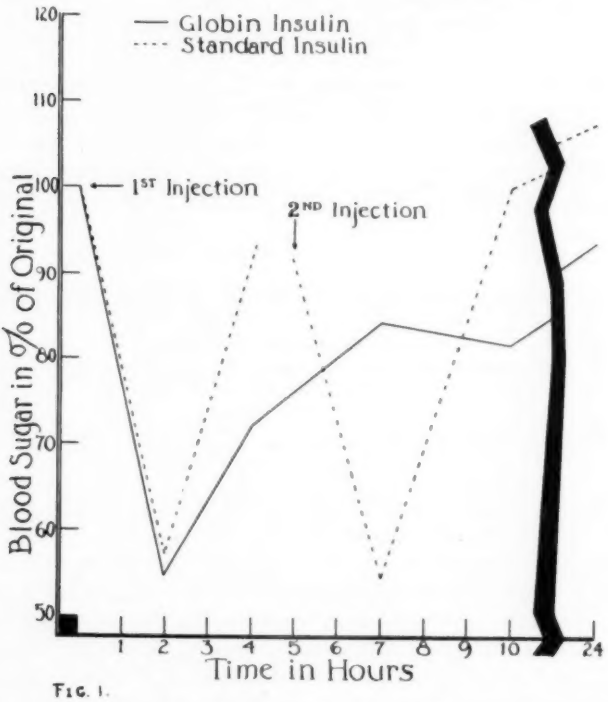

FIG. 1.

FIG. 1.—COMPARISON OF THE EFFECT OF GLOBIN AND REGULAR INSULIN. Globin insulin (0.8 unit per kg.) was injected into 15 fasting rabbits; regular insulin (0.4 unit) was injected into 15 fasting rabbits and repeated in 5 hours. After 10 hours the effect of globin insulin is still apparent, in fact, the normal fasting blood sugar is not reached in 24 hours; whereas after 2 doses of regular insulin the blood sugar values are above normal at this time. To counteract the effect of individual differences in insulin sensitivity, the experiments were reversed or "crossed" after an interval of 1 week.

Our preparation consisted of a mixture of 80 units of insulin per cc. with native globin in the proportion of 1000 units of insulin to 38 mg. of globin and 3 mg. of zinc (as $ZnCl_2$). When used as a suspension it was buffered to a pH of 6.1 with Na_2HPO_4. More than 99% of the insulin in this preparation was found in the precipitate and less than 0.5 unit per cc. was found in the supernatant liquid. We also used a clear globin solution at a pH of 4. Neither animal experi-

ments nor clinical experience showed any difference between the two preparations which would be significant from a practical standpoint.

Animal experiments having excluded toxicity of the globin even in relatively large and repeated doses, we proceeded to study the effect of the globin insulin preparation on normal human beings. In 5 subjects, 10 units injected 15 hours after the last meal, produced a minimum blood sugar in 4 to 6 hours, ranging from 60 to 80 mg.

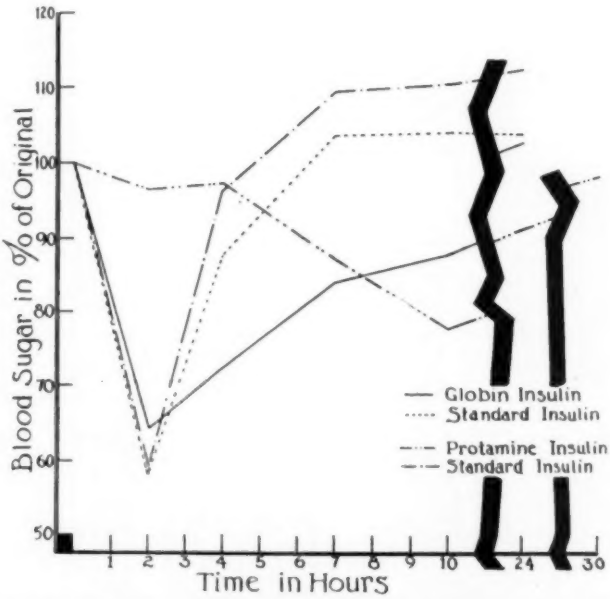

FIG. 2.—COMPARISON OF REGULAR, GLOBIN AND PROTAMINE INSULIN. Injections of 0.5 unit per kg. into each of 30 rabbits. After 1 week the experiment was crossed or reversed as in Figure 1. The effect of standard insulin is spent in 5 to 6 hours. The globin curve is similar to the standard for the first 2 hours; but the effect is noticeable for more than 10 and less than 24 hours. No effect is apparent for the first 4 hours after protamine injection. Maximum activity is delayed for more than 10 hours, and the blood sugar is still below the initial value after 24 hours.

The present communication is based on an experience with this preparation in 25 diabetic patients. A single injection was given 30 to 45 minutes before breakfast. The carbohydrate allotment was usually distributed in varying amounts for breakfast, lunch and dinner, depending on the effect of the insulin and severity of the diabetes. In this study our practice has been to administer the diet suitable to the age, weight and physical condition of the patient and then to adjust the insulin to this plane.

The urine sugar was determined in periods, or, in some cases, each voiding was tested with Benedict's solution. Blood sugars

were estimated as often as four times daily, that is, fasting, before lunch, before dinner, and at 10 P.M.

Whenever possible, periods of administration of the globin zinc insulin preparation were compared with protamine zinc insulin and also with standard insulin. Numerous difficulties are encountered in a comparison of this sort. It is not easy to get otherwise healthy diabetic patients to remain in the ward for a sufficient length of time to obtain adequate comparable periods. Interpretation is obscured

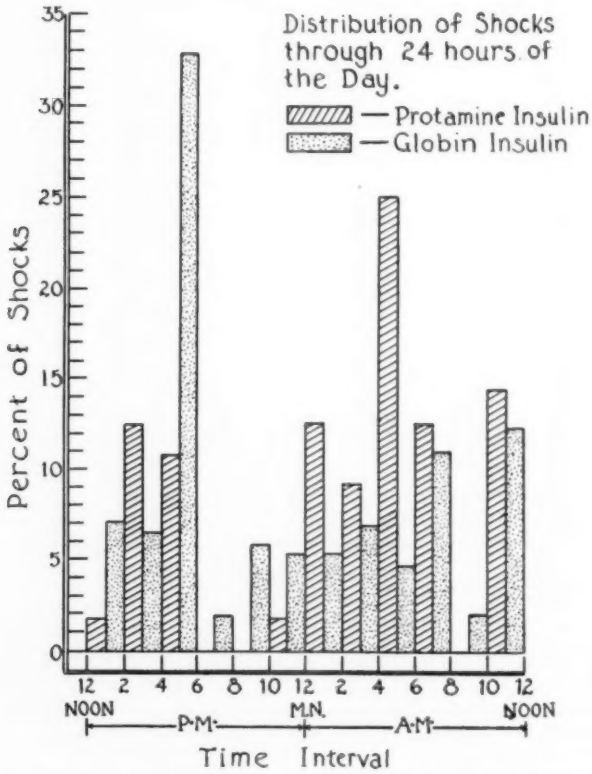

FIG. 3.—Distribution of shocks through 24 hours of the day.

by the cumulative tendency of protamine zinc insulin and by the occurrence of insulin shocks, which are almost unavoidable. In juvenile cases lack of uniform physical activity often confuses the comparison. In a number of instances we have observed what appears to be a temporary increase in the severity of the diabetes after insulin shock. This may be due to a decrease in the insulin-producing activity of the pancreas following the over-supply of the hormone. The bewildering fluctuations in sugar excretion so fre-

quently observed in juvenile patients, when diet and external conditions are apparently unchanged are difficult to explain. We really know little regarding the mechanism of insulin action. Glycogen mobilization and other ferments and coferments that participate in sugar oxidation may be limiting factors. These and other variables make judgment difficult and caution necessary.

TABLE 1.—CASE RECORD COMPARING EFFECTS OF REGULAR PROTAMINE AND GLOBIN INSULINS. Z. L., AGE 60 (HISTORY NO. 508695).

Data of Previous Admission.

Dates, 1937.	Diet. C.	P.	F.	Insulin. A.M.	M.	P.M.	Regulation.
1/22–2/6	100	60	50	20	0	20 R	Good
2/6–2/13	100	60	50	30	0	0 P	Good
2/14–2/20	100	60	50	30	0	0 G	Excellent

Dates, 1938.	Insulin.	Diet. C.	P.	F.	Blood sugars before. Breakfast.	Lunch.	Dinner.	10 P.M.	Urine sugars.
7/16	40 P	120	60	50					
7/18	40 P				110	138	123	140	Sugar free during entire period.
7/28	40 G								
7/31	40 G							118	
8/1	40 G				104	117	72		
8/3	40 G								
8/8	40 G					132	133	126	
8/9	40 G				151				

Comment: Shows the similar effect of protamine and globin insulin on a mild diabetic who is on a low carbohydrate diet.
G = globulin insulin.
P = protamine zinc insulin.
R = regular or standard insulin.

TABLE 2.—CASE RECORD COMPARING EFFECTS OF PROTAMINE AND GLOBIN INSULINS. J. W., AGE 64 (HISTORY NO. 465816).

Data of Previous Admission.

Date.	Diet. C.	P.	F.	Insulin. A.M.	M.	P.M.	Regulation.
August, 1936	200	70	100	10	0	10	Excellent

Date, 1937.	Insulin	Diet. C.	P.	F.	Blood sugars before. Breakfast.	Lunch.	Dinner.	10 P.M.	Urine sugars. 9 A.M.	11 A.M.	1 P.M.	3 P.M.	5 P.M.	7 P.M.	9 P.M.	6 A.M.
5/19	47 P	300	80	80	111	126	121	116	+−	+−	○	○	○			
5/20	36 G					159										
5/21	47 G				116	171	133	170				+−	+−	3+		
5/24	47 G					121	123	125	+−	○	+−	+−	+	○○	○	○
5/27	47 G	210	80	80	94	134	124	119	+	+	+	+	+	+○	○○	○○
5/28	47 G	296	80	80					+−	+−	+−	+	+	○−	+○	○○
5/29	47 G	300	80	80												
6/4	47 G				94	116	91	121	+	2+	○	+	+−	+	○+	+○
6/7	47 P							116	+	+−			+		+○	+−
6/8	47 P				94	123	154		+○	+			+		+−	○
6/14	47 P	294	80	80					+−	+					+−	+−
6/15	47 P	300	80	80					○	+−			+−		+	+−
6/18	47 P					109	110		○	+−			+−		+	+−
6/21	47 P	300	70	80				183	○	+			+−		+−	○
6/22	47 P	300	66	80	326				○	+−			○		+	○
6/23	47 P								○	○			+−		+−	○
6/24	47 P				112	156	200	218	○	○			+		+−	+−
6/26	47 P	300	70	80					○	○					+−	○
6/27	47 P					169	166	172	○	○						○
6/28	35 P	200	76	115					○	○						○
6/29	35 P				148				○	+−						

Comment. If anything, better control on globin insulin.
G = globin
P = protamine zinc insulin
R = regular or standard insulin

Discussion of the Tables. We have used globin zinc insulin in children and adults for about 2 years. The maximum single dose was 145 units. Daily doses of 60 units or more have been injected for about 2 years without any apparently harmful effect. At present, water clear solutions are used.

If the usual morning dose is too large, a hypoglycemic reaction will occur usually in the late afternoon, that is, about 7 to 12 hours earlier than the average protamine shock period.

TABLE 3.—CASE RECORD COMPARING EFFECTS OF REGULAR PROTAMINE AND GLOBIN INSULIN. H. D., AGE 42 (HISTORY NO. 354588). DIABETES DISCOVERED IN 1933.

Data of Previous Admissions.

Dates.	Diet.			Insulin.			Regulation.
	C.	P.	F.	A.M.	M.	P.M.	
9/17/33–9/27/33	100	60	50	30	0	18	Excellent
4/30/37–5/13/37	250	75	100	44	0	22	Good
5/17/37–5/17/37	250	75	100	40	0	40	Good

Dates, 1937.	Insulin.	Diet. C.	P.	F.	Blood sugars before. Breakfast.	Lunch.	Dinner.	10 P.M.	Urine sugars. 11 A.M.	4 P.M.	7 A.M.
12/3	70 G	250	100	75							
12/7	70 G				149	309	233	229	○	+−	+−
12/8	70 G				148	322	204	274	○	○	+
12/10	85 G								○	○	○
12/11	85 G				104				○	○	○
12/13	85 G				71				○	○	○
12/14	82 G								○	○	○
12/15	82 G				67	145	118	96	○	○	○
12/16	82 G				110	172	106	95			

Comment. Since discharge about 11 months ago she has visited the clinic about 21 times. Regulation has been quite satisfactory.

G = globin.
P = protamine zinc insulin.
R = regular or standard insulin.

In certain cases, usually severe, and especially juvenile cases, the same unexplained daily variation in sugar excretion is encountered as when the regular or protamine preparations are used. The charts and other observations (omitted for lack of space) indicate that a single daily dose of globin insulin will regulate the mild and moderately severe cases. In those severe cases requiring 100 or more units daily, complete control was often impossible during the entire 24-hour period. Periods of hyper- and hypoglycemia may be unavoidable, but they often occur when several doses of standard insulin are used, and certainly when a single dose of protamine insulin is administered. However, we have encountered several cases, uncontrollable with protamine zinc insulin, which were regulated to greater satisfaction with single doses of 80 to 120 units of the globin compound.

Globin zinc insulin is less apt to produce shocks during the night than protamine zinc insulin (Fig. 3).

We sincerely believe that the behavior of globin zinc insulin warrants further trial by clinicians especially trained in the management of diabetic patients.

TABLE 4.—CASE RECORD COMPARING EFFECTS OF REGULAR, PROTAMINE AND GLOBIN INSULINS. R. H., AGE 19 (HISTORY NO. 309995).

Data of Previous Admissions.

Date.	Diet.	Insulin (standard).	Regulation.
October, 1931	248–100–20	10–0–3	Fair
January, 1932	220–70–100	14–0–7	Fair
Seen in Out-Patient Department until admitted			Poor
July, 1933	200–70–100	55–0–20	Fair

Followed in the Out-Patient Department until the admission recorded below. Patient's urine has almost always showed large quantities of sugar even when receiving 65–0–25 units of insulin (Standard).

Date, 1939.	Insulin.	Diet. C.	P.	F.	Blood sugars before. Breakfast.	Lunch.	Dinner.	10 P.M.	Urine sugars. 9 A.M.	11 A.M.	1 P.M.	3 P.M.	5 P.M.	7 P.M.	9 P.M.	6 A.M.
2/2	20 S 45 P	180	80	80	286					4+	2+	0	0	0	0	4+
2/9	30 S 60 P	180	80	80			115		4+	2+	0	0	0	0	2+	+
2/10	30 S 60 P	180	80	80	200				+	0	0	0	0	0	+	0
2/11	30 S 60 P	200	80	80					+	0	0	0	0	0	0	0
2/13	30 S 60 P	250	80	80					0	0	0	2+	+	+	+	0
2/14	30 S 70 P	250	80	80					0	0	0	+	0	2+	4+	2+
2/16	15 S 70 P	250	80	80	111	59	54	78	2+	+	0	0	0	+	0	0
2/21	85 P	250	80	80					+	3+	4+	4+	4+	3+	4+	2+
2/22	85 P	250	80	80					+	2+	2+	4+	+	0	0	0
2/23	85 P*	250	80	80	48				+	3+	4+	4+	3+	0	0	0
2/24	85 P	250	80	80					0	+	+	3+	0	0	4+	3+
2/25	85 P	250	80	80					+	0	+	4+	4+	2+	4+	3+
2/26	85 P	250	80	80					+	0	0	0	0	0	0	0
2/27	85 P	250	80	80	100	179	160		0	3+	3+	4+	3+	2+	3+	4+
2/28	85 G	250	80	80					3+	3+	+	0	0	0	0	0
3/1	85 G	250	80	80					0	0	0	0	0	0	0	0
3/2	85 G	250	80	80					0	0	0	0	0	0	0	0
3/3	75 G†	250	80	80			82	144	0	0	0	0	0	0	+	0
3/4	75 G	250	80	80	108	177			0	0	0	0	0	0	+	0
3/5	75 G	250	80	80					0	0	0	+	0	0	0	0
3/6	75 G	250	80	80					+	2+	3+	3+	2+	2+	2+	+
3/7	75 G	250	80	80			44	89	+	+	0	0	0	0	0	0
3/8	75 G	250	80	80	74	55			0	0	0					

* Hypoglycemic shocks at 11 P.M., 2 A.M., 6:35 A.M.

† Hypoglycemic shock at 5 P.M.

Comment: The regulation of this patient was fairly satisfactory on a double dose of standard and protamine insulin. On a single dose of insulin, however, the regulation was better with globin than protamine insulin. Patient discharged on 65 units of globin insulin.

G = globin P = protamine zinc insulin R = regular or standard insulin.

Summary. The effect of a single daily dose of a clear solution of globin insulin was studied in about 25 cases of diabetes in a period of about 2 years.

1. No skin reactions were observed.
2. Mild and moderately severe cases were adequately controlled.
3. Several cases uncontrollable with protamine zinc insulin were controlled fairly well with the globin compound.

The coöperation of Drs. Edgar Stillman, Bertram J. Sanger, Henry E. Marks and Rudolph Scharf of the Metabolism Service of the Presbyterian Hospital is gratefully acknowledged.

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PREDICTION AND PREVENTION OF LATE PREGNANCY ACCIDENTS IN DIABETES.

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The problem of pregnancy complicating diabetes has been of great interest to us, for unlike other complicating diabetic situations the continued use of insulin did not solve it. Until recently it has been nearly as true of the insulin as of the pre-insulin era that only every other diabetic pregnancy terminated successfully. The accidents common in diabetic pregnancies do not concern the welfare of the mother, for maternal mortality is and should be low, but do concern the welfare of the child destroyed, by: 1, early spontaneous abortion, miscarriage or premature birth; 2, stillbirth; and, 3, a neonatal type of death common within 24 hours of delivery.

This statement is based upon a study of the records of 353 pregnancies in 242 diabetic women who have been under our care since 1898. The number includes patients who were treated by us during pregnancy and also those patients who were treated elsewhere during this period and consulted us at some later date. Excessive fetal mortality rates have been reported by all authors of obstetrical diabetic literature. Even when we confine our studies to reports of the year 1938 when we would expect to find the benefit of most modern treatment of diabetes, discouragingly high fetal mortality rates are reported by Johnstone,[7] Potter and Adair,[11] Brandstrup and Okkels,[2] and Herrick and Tillman.[5]

From Table 1, in which are tabulated all cases with known outcome in the pre-insulin and insulin eras, it is evident that excluding surgically interrupted pregnancies the fetal mortality in the pre-insulin era was 44% and in the insulin era 38%. In the pre-insulin era, early and late fetal deaths occurred with equal frequency. In the insulin era, 60% of the fetal deaths were late, due to stillbirth or neonatal accidents and 40% to spontaneous abortions. The prob-

lems are therefore of nearly equal importance, but the late pregnancy accidents lend themselves to study whereas the early ones do not. This is true because so often the patient early in pregnancy reports for medical care only after incomplete abortion. For this reason, it has been our chief concern to investigate the cause and the means to prevent late accidents of diabetic pregnancies.

TABLE 1.—OUTCOME OF 353 PREGNANCIES IN 242 DIABETIC WOMEN.
(Analysis based on histories as well as experience of George F. Baker Clinic.)

Era.	Total No.	Live births.	Neonatal deaths.	Stillbirths.	Abortion or miscarriage.	Therapeutic abortion.
Pre-insulin	108	57	0*	23	23	5
Insulin	245	142	24	27	35	17

* Undoubtedly neonatal deaths occurred in the pre-insulin era. The data based on records going back to 1898 and based on case histories cannot be as accurate as more recent ones and those based on actual experience.

For years, and quite naturally, too, the authors of obstetrical diabetic literature have attributed these accidents to diabetes *per se*, its complications or its treatment. As a longer interval of time has passed we have not been able to agree with the opinion that the accidents of diabetic pregnancies are caused by faulty management of the disease, diabetes, nor can we agree with the opinion that they can be prevented by adequate control of the diabetes. We have seen that severe diabetic crises—coma and hypoglycemia—are not at all incompatible with the birth of a living child. Thus among 14 accidents in late pregnancy, maternal coma occurred only twice, in each instance precipitated by infection, and the remaining 12 patients had no signs of acidosis. These latter had taken meticulous care of their diabetes to insure the birth of a living child. In contrast to this experience other patients careless of the diabetic routine have had successful outcome of the pregnancy. For this reason we have been stimulated to search for some extradiabetic factor common in diabetic pregnancies.

The first suggestion of a possible hormonal imbalance in diabetic pregnancies was made in 1933 by Murphy[10] who reported that the prolan excretion of 2 diabetic women exceeded the normal. This work was carried much further by Smith and Smith[12a,b] who, evaluating the problem of hormones in pre-eclamptic toxemia of pregnancy, quite naturally turned to our diabetics in order that they might study the problem from early to late pregnancy since the incidence of toxemia in diabetes was known to be great. They had observed that an excess of serum prolan (anterior pituitary-like substances) precedes and predicts pre-eclamptic toxemia. These observations were confirmed in the toxemic diabetic.

But along with these very important biochemical observations, equally important clinical correlations became evident to us; first, that stillbirth, the most dreaded accident in diabetic pregnancies, was not related to diabetes or its specific complication, coma, but was definitely related to pre-eclamptic toxemia and as time elapsed that the accidents—neonatal death and premature delivery—were also related to the abnormal hormone picture. The relationship of toxemia and stillbirth first became apparent to us when, in order to obtain specimens for biochemical research, the patient reported to us at almost daily intervals. We then observed that in many diabetic women the course of pregnancy was uneventful until the sixth month; at any time thereafter, that the patient often developed edema, albuminuria and a rising blood pressure. Early in our experience we found that shortly after the rise of the blood pressure the fetus died and thereupon the signs of toxemia promptly disappeared. The entire clinical picture can occur and disappear in as short a period of time as 1 week, but we now know is predicted some 4 to 6 weeks by the rise of the serum prolan.

Between January, 1936, and March, 1939, 35 completed pregnancy cases have been studied with examinations for serum prolan. At first, as a part of the studies by Smith and Smith, later because we were convinced of its value, we adopted it as a routine laboratory procedure.

Method. The laboratory procedure as worked out on a routine basis is as follows: Beginning with the 24th week of pregnancy or as near that time as can be calculated by the irregular data of the patient, determinations of serum prolan are made each week or each 5 days if indicated by high results. The serum is precipitated with alcohol, the precipitate is extracted with ether which removes the estrin and the remaining precipitate is taken up in suspension with 6 cc. of normal saline. One cubic centimeter of the saline suspension is injected twice a day for 3 days into immature female white rats 21 to 23 days old weighing 30 to 35 gm. On the fifth day after the initial injection the ovaries are examined. A positive test is indicated by the presence of corpora lutea. The results are recorded in terms of "rat units." The prolan present in 1 cc. of serum is considered as 100 rat units per 100 cc. of blood; 0.5 cc. equals 200 rat units.

Our routine procedure consists of running duplicate tests for 200 R. U. If positive findings result from injection of 0.5 cc. of serum, the test is repeated using smaller amounts of serum.

The details of the biochemical research, the relationship of this problem to pre-eclamptic toxemia, will be reported by Smith and Smith. It is our purpose here to summarize the clinical course of the patients studied and to give the coincidental condition of the child; second, to present evidence that this laboratory test predicts the accidents common in diabetic pregnancies, and, third, to summarize the end-results of patients treated with replacement estrin and progestin therapy.

The 35 patients studied may be logically divided into 4 groups: first, 14 patients whose values for serum prolan were repeatedly normal (namely, less than 200 rat units per 100 cc. of blood from

the 6th to the 8th month); 10 patients whose values for serum prolan were supernormal and which rose steadily to term; 2 cases whose values were supernormal but which fell steadily; and 9 patients whose values were supernormal but who received replacement therapy. In Table 2 the 35 patients are classified according to the highest late prolan values. In addition, the average blood sugar and insulin are listed according to each trimester; also, the values for carbon dioxide combining power, and the lowest value for plasma protein. Data on the clinical signs of toxemia, duration and outcome of the pregnancy and the type of delivery are also included.

Of the 35 patients carefully studied, 9 were former juveniles—patients with onset of diabetes under 15 years of age. Only one had onset of diabetes during pregnancy and only one required no insulin. Twenty-six had severe or moderately severe diabetes. One patient developed coma, one had a 3-day interval of hypoglycemia following the mistaken administration of 276 units of protamine zinc insulin. In general, the control of diabetes was good in all patients.

Clinical Course of the Pregnancy. The clinical course of the 14 patients whose values for serum prolan were repeatedly normal was completely uneventful. None developed toxemia, none miscarried. Quite different was the clinical course of the 10 patients whose values for serum prolan were supernormal and who received no therapy. All developed complications. Seven developed toxemia. The remaining 3 delivered themselves prematurely. All toxemic patients were hospitalized, treated with rest, low-salt, high-protein diets and supplementary vitamin B and calcium, yet progressive toxemia was the rule.

Of greatest interest to us was the clinical course and biochemical behavior of the 2 cases—successive pregnancies in the same patient whose values for prolan fell. This fall of prolan was preceded by a rise of estrin which was noted some 4 weeks prior to the normally expected time. During the first[12c] pregnancy she developed well marked signs of toxemia which decreased in severity with the fall of prolan. Less well defined signs in the second pregnancy disappeared entirely. The biochemical behavior of this patient gave further presumptive evidence of the probable value of estrin therapy.

On the advice of Smith and Smith the next group of patients, whose values for serum prolan were supernormal, received massive doses of estrin, 150,000 to 300,000 international units as progynon B and in addition progestin, in the form of 10 to 20 mg. of proluton daily* (in a few instances testosterone was substituted for progestin). The rationale for progestin therapy[12d] is substantiated by the demonstration of a lowered excretion of sodium pregnandial glucuronidate. Brown, Henry and Venning[3] have also found low estrin and diminished pregnandial excretion in pregnancy toxemia. Weil[15] has also reported lowered pregnandial excretion in toxemia.

* Progynon B and Proluton were supplied to us through the courtesy of the Schering Corporation.

TABLE 2.—COMPARISON OF THE CLINICAL COURSE OF PATIENTS WHOSE VALUES FOR SERUM PROLAN WERE STUDIED.

Case.	Duration, yrs.	Pregnancy, age.	Blood sugar, mg. %, trimester.			Insulin units, trimester.			Diab. complic.	Plasma CO_2 combining power, vol. %, trimester.			Serum prot., mg.	Gain wt., lbs.	Edema.	Albumin.	Blood pressure, trimester.			Subject. symp.	Prolan, R.U. per 100 cc. blood.	Dur. preg., wks.	Outcome.	Hypoglycemia.	Asphyxia.	Weight, lbs.	Type of delivery.
			1.	2.	3.	1.	2.	3.		1.	2.	3.					1.	2.	3.								
I.													(a) *Hyperprolanemia Untreated.*													
1	14	26	.11	.10	..	30	28	..	0	..	35	..	5.3	35	+	400	100/80	180/120	....	+	775	27	N.N.	..	+	6.8	C
2	4	20	..	.17	.18	..	60	42	0	..	50	45	..	13	+	500	....	120/80	172/104	+	666	37	L.B.	0	0	5.4	C
3	10	29	.10	.13	.12	..	..	60	0	..	..	35	..	27	+	500	...	....	160/108	+	666	35	L.B.	0	0	6.8	C
4	3	29	.22	.18	.10	26	28	68	0	44	32	46	..	48	+	tr.	...	....	150/90	0	666	35	L.B.	0	0	10.8	C
5	7	33	.20	.17	.24	64	72	106	0	..	..	..	..	30	+	20	120/80	100/60	180/80	0	333	37	L.B.	0	0	9.1	C
6	3	31	..	.16	..	..	32	..	0	..	50	..	..	30	+	tr.	...	160/110	....	+	200	30	S.B.	..	..	..	N
7	10	33	.12	.19	.19	50	30	0	0	53	41	30	..	31	+	l.t.	130/80	130/80	200/90	+	200	37	S.B.	..	..	10.0	C
8	.8	25	.15	.18	.13	18	20	10	0	..	42	37	..	20	0	v.s.t.	116/54	116/60	130/80	0	200	32	N.N.	0	+	7.0	Sp.
9	4	29	..	.19	..	..	36	..	0	..	32	..	..	..	+	0	...	120/80	....	0	200	30	N.N.	..	+	3.0	Sp.
10	3	25	..	.16	.22	..	46	44	0	..	48	49	..	6	0	0	...	130/80	120/80	0	200	32	N.N.	..	..	4.8	Sp.
II.													(b) *Hyperprolanemia Self Corrected.*													
11	5	25	.11	..	.11	20	20	20	0	..	49	46	..	27	+	l. tr.	110/80	104/64	150/80	+	500	39	L.B.	0	0	8.7	C
12	7	27	.20	.16	.12	20	42	42	0	48	50	43	..	23	+	30	120/80	100/60	130/80	+	500	36	L.B.	0	0	7.9	C
III.													(c) *Hyperprolanemia Treated.*													
13*	6	35	..	.15	.20	..	35	60	+	..	50	45	..	22	+	tr.	...	130/80	150/110	+	500	34	L.B.	+	+	7.8	C
14	4	16	..	..	.13	..	..	60	0	..	..	51	6.5	17	+	130	...	....	150/120	+	500	38	L.B.	0	0	5.2	C
15	12	35	.15	.19	.15	40	60	80	0	49	39	42	4.7	20	+	30	148/80	120/80	140/80	+	500	36	L.B.	0	0	8.4	C

16	2	37	..	..	.14	..	..	100	+	..	..	..	5.1	0	+	280	...	....	130/80	+	500	?	S.B.	..	..	..	N
17†	5	26	..	..	.14	..	..	80	+	..	..	35	5.1	4	+	400	...	....	180/100	+	333	37	L.B.	0	0	4.8	N
18	21	31	.10	.11	.15	58	76	76	0	..	..	47	5.2	23	+	60	118/70	130/80	150/110	+	333	36	L.B.	0	0	6.2	C
19	4	25	..	.15	.11	..	52	46	0	..	48	47	6.0	11	+	80	...	120/80	120/80	+	333	37	L.B.	0	0	7.7	C
20	17	25	.11	.12	.17	74	70	90	0	..	38	32	4.6	12	+	50	110/60	100/70	140/80	+	333	37	L.B.	0	0	6.9	C
21	10	23	..	.16	.17	50	50	80	0	..	..	31	5.4	14	+	50	...	110/80	120/80	+	333	37	L.B.	+	0	7.2	C
IV.													(*d*)	*Normal*		*Prolanemia.*										
22	6	18	.15	.08	.15	60	42	84	0	49	52	50	..	13	0	10	130/80	....	120/90	0	50	..	L.B.	0	+	7.4	C
23	8	20	.10	.16	.13	46	44	54	0	51	46	49	5.0	21	+	v.s.t.	130/80	100/60	120/80	0	100	..	L.B.	0	0	6.8	C
24	4	36	.09	.09	.10	0	..	0	0	..	..	..	..	23	+	0	100/70	120/80	100/80	0	<200	37	L.B.	0	0	7.8	N
25	16	25	..	.14	.13	..	46	54	0	47	48	39	..	25	0	s.p.t.	...	110/80	120/80	0	150	..	L.B.	+	+	6.4	C
26	4	32	.12	.21	.17	36	58	96	0	..	..	..	..	22	0	s.p.t.	120/70	120/80	90/60	0	100	38	L.B.	+	0	7.0	C
27	6	21	..	.15	.09	..	64	44	0	..	43	..	6.4	8	0	10	...	120/60	124/80	0	<200	..	L.B.	0	0	7.5	C
28	4	23	.17	.18	.13	42	48	54	0	..	43	..	..	31	+	30	120/80	120/80	120/80	0	100	35	L.B.	+	+	8.8	C
29	7	28	.12	.12	.15	32	40	43	0	..	45	47	..	10	+	s.p.t.	...	110/60	112/78	0	150	36	L.B.	0	+	5.0	C
30‡	5	31	..	.17	.11	..	33	42	0	..	45	41	5.6	25	+	80	...	104/70	110/80	0	100	38	L.B.	+	0	8.3	C
31	7	37	.29	.19	.13	60	46	52	0	..	45	40	..	45	+	30	130/70	120/80	150/80⁺	0	100	38	L.B.	0	0	10.6	N
32§	3	37	.17	.18	.13	25	25	25	0	50	52	52	..	12	+	10	120/80	160/110	150/90	0	100	34	N.N.	0	+	8.0	C
33§	.5	36	..	.17	.19	20	20	0	0	..	41	44	..	0	+	50	...	140/80	170/120	0	100	..	L.B.	0	+	6.9	N
34§	9	38	.11	.19	.10	28	24	12	0	..	47	44	..	15	+	15	140/80	140/80	170/80	0	50	37	L.B.	0	0	8.8	N
35	5	32	.25	.22	.15	40	41	66	0	..	37	48	5.8	26	+	0	120/80	110/80	120/80	0	<200	39	L.B.	0	0	8.4	N

* Coma. † Pyelitis. ‡ Pulmonary tuberculosis and pyelitis. § Known hypertensive. ⁺ One reading only.

Comparison of the clinical course of patients whose values for serum prolan were: (1) supernormal untreated; (2) supernormal self corrected; (3) supernormal treated with replacement therapy; (4) normal.

L.B. = Live birth.
S.B. = Stillbirth.
N.N. = Neonatal.
C. = Cesarean section.
N. = Normal delivery.
Sp. = Spontaneous premature delivery.

The purpose of this therapy was twofold: Prevention as well as correction. For this reason, patients so treated include those whose values for prolan were repeatedly supernormal and who had developed all signs of toxemia and those with few suggestive signs. Thus of the 9 patients 4 had hypertension, albuminuria, edema, pain, headache, or nausea and vomiting. One patient had all signs and symptoms except hypertension; 3 had albuminuria and edema and one edema only.

Replacement therapy was followed by a drop in serum prolan controlled by the size and frequency of the dose of hormones. No instance of progressive toxemia occurred. Not one miscarried. There was a tendency for the serum protein which fell to low levels to rise without change in diet, the weight to fall, the urinary output to be increased, the albumin to be diminished and the blood pressure to fall.

Fetal Mortality. Of greater importance in our diabetic problem, however, is the apparent effect of the abnormal hormone picture, upon the child. Fetal deaths in this group of 35 patients occurred with one exception among the patients whose values for serum prolan were supernormal. Thus among our 14 infants of mothers whose values were normal there was 1 death (7%). This death occurred 2 hours after delivery and was classed as asphyxia pallida. The autopsy was negative. A strong lethal factor was suspected, because there was not only maternal diabetes but grandmaternal diabetes on both sides of the family.

In contrast to the low mortality rate of 7% in infants of diabetic mothers whose values for serum prolan were normal, is the high rate of 60%; 6 of the 10 infants, whose mothers' prolan values rose steadily to term. These deaths occurred three times in relation to toxemia and three times in relation to premature delivery. The positive findings at autopsy were hemorrhage into the adrenal, once, in the only infant who survived toxemia; erythroblastosis among the premature infants, once; inanition once and hematopoiesis of the liver once. The remaining 2 infants were macerated.

In contrast to the high fetal mortality in the group of patients whose values for serum prolan were supernormal and who received no therapy, was the low mortality of those who received replacement estrin and progestin therapy (150,000 to 300,000 international units of estrin, 10 to 20 mg. progestin per day). Eight of the 9 had successful outcome. Because of the high cost of treatment under usual conditions, we reduced therapy in the ninth patient after the prolan had reached normal values. A typical intra-uterine fetal death followed after a rise of prolan.

As a control the past obstetrical histories of these patients are of interest, because in diabetes the pattern of the pregnancy is usually repeated. Four of the 9 were primiparæ, 3 were known and 1 suspected previously to have had toxemia, all with stillbirths. In addition, 2 had miscarried. The only patient who had a living

child previously was the one whose therapy was reduced and finally omitted. The living child had been born 4 years prior to the onset of her diabetes. The most remarkable patient in the group was Case 1469, whose diabetes was of 21 years' duration and who had hemorrhages and exudate of the retina with clinical signs of toxemia. These signs disappeared after 1 week's therapy.

In addition to the 35 cases whose serum prolans have been studied, 21 late pregnancy cases were followed and delivered by us. Of the 22 infants (one twin pregnancy), 16 survived. Three of the deaths occurred *in utero* and 3 on the first day of life. Of the stillbirths 2 occurred in well controlled cases; 1 in a patient who developed coma during labor but since the fetus was born macerated, we believe it died prior to the coma. Of the 3 neonatal deaths 1 occurred at 24 weeks during severe lobar pneumonia and mild diabetic coma.

In addition to a high mortality rate, the infants of diabetic mothers are predisposed to asphyxia, gigantism, congenital defects and hypoglycemia.

Congenital Defects. In this small group of 35 patients, congenital defects occurred 3 times. One child had a club foot, claw hand, web toes and missing fingers and in addition is probably feeble-minded; another had a congenital heart lesion and a third congenital luxation of both hip joints. All occurred in the abnormal hormone group, 2 among patients who received treatment.

Hypoglycemia. Hypoglycemia occurs, but in our experience it has never been a fatal accident. Blood sugar studies (127) have been done on 38 infants; 40 were 60 mg. or less—of these 20 were 60, 10 were 50, 3 were 40, 6 were 30, and 1 was 9 mg. Of the 38 patients, 7 had one determination for blood sugar only. Of the 31 patients with repeated tests, 21 had values less than 70 mg., 23 received no glucose, 15 received glucose. Clinical signs of hypoglycemia were encountered once. Infants of diabetic mothers do have hyperplastic islands, but stabilization of the sugar in the blood occurs on the second or third day and hypoglycemia may be related to maternal insulin. There was no correlation between hypoglycemia and prolan values.

The level of the blood sugar of newborn infants was studied by Kitteringham and Austin[8] who found, using the modified Folin-Malmos technique, that the level of the blood sugar of normal infants varies from 55 to 75 mg. on the first 2 days and reaches higher levels on the third. A drop of blood sugar level occurs within 3 to 6 hours after birth. This experience is similar to that found in the infants of diabetic mothers. Thus only 10 of the blood sugars out of our 127 determinations, or a total of 9 infants out of 38, had levels of blood sugar lower than infants of normal mothers. McKittrick[9] studied infants of normal mothers and came to similar conclusions. His lowest value was 28 mg. in an infant whose behavior was entirely normal.

Asphyxia. Asphyxia in its fatal form, with 1 exception, occurred in infants whose mothers' values for serum prolan were supernormal.

Gigantism. Gigantism or "over-ripeness" has been reported as characteristic of infants of diabetic mothers. Of 91 infants in our series 42 weighed more than 8 lbs. and 22 weighed less than 7 lbs. Authors of obstetrical diabetic literature have attributed the large size to hyperglycemia. This tendency for gigantism, however, may be related to abnormal hormone picture in that weights appear to be controlled in the treated group and this is further suggested by the independent experiments of Teele, Snyder and Hoopes[6,13a,b,14] who have injected prolan into pregnant rats and rabbits and have produced a result not unlike a diabetic pregnancy, miscarriage, stillbirth overdevelopment, death and maceration of the giant fetus! Snyder[13b] has shown by the intravenous injection of prolan into rabbits in the last quarter of pregnancy that when a new set of corpora lutea were induced on the 25th day a premature separation of the placenta occurred in certain implantations whereas those adjacent were still adherent and destined to persist 9 days post-term. He thinks that edema and actual endometrial growth associated with the development of a new set of corpora cause sufficient structural changes in some of the placentæ to dislodge them. Such dislodgment is always associated with uterine bleeding. The young may be born alive. In like manner, Bøe[1] showed prolongation of pregnancy with fetal weight increase in rats. Hyphophysectomy produced the same prolongation in some instances with striking increase in fetal weight. But weight increase cannot be explained on the basis of prolongation of pregnancy for mechanical obstruction by ligature of uterine horns did not cause an increase in fetal weight. In his analysis of uterus, fetus and placenta during prolonged gestation, he reaches the conclusion that the fetal death resulted from failure of the placenta.

The relative size of the infants in our series is shown in Table 3. Since we have elected premature delivery in many cases we have undoubtedly lowered average weights somewhat. The greatest relative average weight was 7.1 lbs. in the 33d week among the supernormal prolan untreated cases. The lowest relative and absolute average weight occurred in the group of patients whose values for prolan were supernormal but who received hormone therapy, namely, 6.8 lbs. in the 36.5th week of pregnancy. The effect of prolonged high estrone dosage on impaired body growth was first shown by Zondek.[16]

Discussion and Summary. No attempt to explain the mechanism of the abnormal hormone picture in diabetic pregnancies is made here. Before determinations for prolan were routinely done in our clinic, the pregnant diabetic was a nightmare to us, for we never knew by severity, duration, age or control of diabetes which patient might be expected to progress satisfactorily and which might be expected to miscarry or have an intra-uterine death. The test for

prolan permits us to classify the patients according to hazard and to gauge the effect of therapy.

TABLE 3.—COMPARISON OF THE OUTCOME OF DIABETIC PREGNANCIES IN (*a*) PATIENTS WHOSE SERUM PROLANS WERE NOT STUDIED; (*b*) THOSE WHOSE VALUES WERE NORMAL; (*c*) SUPERNORMAL UNTREATED; (*d*) SUPERNORMAL TREATED.

	No. of cases.	Dur. of diab. av.	Age preg., av.	Bl. sugar, mg. %, trimester.			Insulin, units, trimester.			CO_2 combining power, vol. %, trimester.			Wt. gain lbs.	Preg. dur., wks.	Baby's wt., lbs.	Live births.	
				1.	2.	3.	1.	2.	3.	1.	2.	3.				No.	%
(a) No prolan data* Control group Consecutive cases	20 (1 twin)	5.0	29	.14	.17	.16	25	40	30	33	23	38	26	37	7.7	16	76
(b) Normal prolan	14	6.0	30	.15	.16	.13	38	40	52	49	45	45	21	37	7.6	13	93
(c) Supernormal prolan Untreated†	10	5.8	28	.15	.16	.17	37	39	47	48	41	40	27	33	7.1	4	40
(d) Supernormal prolan Treated	9	9.0	28	.12	.15	.15	55	57	74	49	44	41	15	36.5	6.8	8	90

* Excluded 2 for inadequate data. † Excluded 2—self corrected.

Out of 14 patients whose values for serum prolan were normal, none developed pre-eclamptic toxemia, none miscarried and there was one fetal fatality. Out of 10 patients whose values were hypernormal and who received no therapy, 7 developed toxemia, 3 miscarried and there were 6 fetal fatalities. Except for subsiding toxemia the 2 instances of self corrected hyper-prolanemia were uneventful. Out of the 9 treated cases, 8 had toxemia which subsided, none miscarried and there was one needless fetal death, the case where therapy was omitted.

TABLE 4.—UNFAVORABLE OUTCOME. (NUMBER AND TYPE.)

Year.	No. of cases.	Still-birth.	Neonatal death.	Total, %.	Delivery, type.	
					Cesarean.	Normal.
1925–31	12	2	1	25	3	9
1932–35	13	2	3	38	8	5
1936–37	16	1	4	31	11	5
1938–39	17	1	0	6	11	6

The effect of our knowledge and therapy upon the outcome of diabetic pregnancies is shown in a comparison of cases by years. Long familiar with the late intra-uterine death of the fetus but before the present concept of endocrine imbalance, premature delivery by Cesarean section was elected. By this procedure alone there was no favorable effect upon the outcome of the pregnancy, as shown by the almost constant rate of fetal deaths up to the year 1938. The result of estrin and progestin therapy is reflected by the drop from 30 to 6% mortality in our 1938 to 1939 experience. As we gain confidence, the number of Cesarean sections will probably be reduced.

The technique for the test is relatively simple, but the cost of therapy great. However, present experience seems to indicate that inexpensive, oral preparations of synthetic estrogens, namely, DAES,[4] may also prove of value in the treatment of these patients.

Conclusions. Accidents of diabetic pregnancies in 35 consecutive cases studied for serum prolan values from 1936 to 1939 were not related to control of diabetes or its specific complication, coma. With one exception, stillbirth, neonatal deaths and miscarriage occurred among those patients whose values for serum prolan were supernormal. Hypoglycemia and congenital defects in this series were not fatal accidents. Against the abnormal hormonal balance measured by the serum prolan, the diabetic woman appears to have a good defensive mechanism, destroying the offending placenta and incidentally the child, accounting for the high incidence of stillbirth, or expelling the placenta and the child, accounting for the high incidence of miscarriage. Replacement estrin and progestin therapy in a small group of patients was followed by the restoration of the normal value for serum prolan and the successful outcome of the pregnancy.

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ERYTHROPOIESIS FOLLOWING BLEEDING PEPTIC ULCER.

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Hemorrhage is the most common major complication of peptic ulcer, yet despite its importance and frequency there still exists a wide variety of opinion regarding the problems of its prognosis,

course and treatment. The literature has dealt mainly with the problem of the emergency resulting from the hemorrhage. Very little information has been reported concerning the course and the prognosis of the patients who survive the acute episode.

The present paper, based on the records of 237 admissions to this hospital of patients with peptic ulcer, is an attempt to aid in the evaluation of the problems presented by the anemia that follows the bleeding. Special attention has been given to the symptoms resulting from the hemorrhage and the rate of recovery of the red blood cells after the bleeding episode.

All admissions from 1913 to 1936 were included that satisfied the following criteria: 1, Roentgen ray or postmortem evidence of peptic ulcer or a clinical diagnosis of a peptic ulcer based on a typical long standing symptomatology; and, 2, a definite history of melena or hematemesis either within a month before entry or during the hospital stay.

Sex and Age. The group comprised 46 females and 191 males ranging in age from 12 to 80 years. Of the males 47% were from 40 to 59 years while only 34% were below 40. This agrees essentially with the figures for age distribution found in other series.[3,5,8a] In the relatively small group of females, however, the age distribution was slightly different, 50% being below 40 years of age.

Location. The site of the lesion was definitely determined in a surprisingly large number of these cases, 204 of the 237 studied. Of these, 77% were duodenal, 14% gastric and the remainder either gastric and duodenal combined or jejunal.

Symptoms. Detailed accounts of the symptoms of the bleeding episode were obtained in 175 cases. The most common initial symptom was melena, which was noted in 54 cases. Evidence of exacerbation of the activity of the ulcer prior to bleeding usually was not present. Only 47 patients complained of increased pain, nausea, vomiting or epigastric distress before the hemorrhage occurred.

In a large group of patients (42 of the 175) the first suggestion of bleeding were the complaints of weakness coming on rather rapidly, syncope or dyspnea. These symptoms, resulting from the anemia or sudden loss of blood volume, preceded the tangible evidence of bleeding by 2 to 4 days in several cases. In addition to this group, 23 of the cases with exacerbation of activity of the ulcer as the first symptom of the bleeding episode presented the symptoms of blood loss mentioned above before either hematemesis or melena were noted. From this it seems that over one-third of the cases have symptoms resulting from blood loss as the first indication that a hemorrhage has taken place. Complaints of weakness of rapid onset in a patient with an ulcer history should suggest at once a bleeding episode despite the absence of other evidence of bleeding (*i. e.*, hematemesis or melena).

Hematemesis, though a common symptom later in the course of the bleeding episode, was not very frequently the initial complaint, only 32 out of 175 cases. It was an initial symptom in gastric ulcers slightly more frequently than in duodenal ulcers.

Syncope was one of the early symptoms of the bleeding episode that occurred in a fairly large proportion of the cases. It developed in 54 of the 237 cases, and in 21 of these it appeared before any tangible evidence of bleeding was noted. In 11 cases it was the initial event. Apparently the severity of the anemia at the time had no strict relationship to the appearance of syncope, for 32 of the cases had red blood cell counts on admission greater than 3 million. It seems more probably related to the vasomotor instability of the individual and the sudden blood loss. Though it occurred with slightly greater frequency in the older age groups, 41% of the cases were under 40 years of age, and of these one-half had admission red blood cell counts above 3 million. Thus it appears that the presence of syncope by no means indicates an especially severe hemorrhage either in a young or an old individual. It is also evident that syncope like weakness may be the first indication of a hemorrhaging ulcer.

Duration of the Ulcer Symptoms Before Hemorrhage. In an effort to determine if there was any relationship between the chronicity of the ulcer and the bleeding episode, the duration of the ulcer symptoms prior to the bleeding episode was noted in all cases. It was interesting to find that in each decade between 20 and 60 years of age 25 to 30% of the patients had had symptoms for less than 1 year. About 21% of the cases over 60 years had had symptoms for less than 1 year. About 30% of the individuals in each decade over 30 years had had ulcer symptoms more than 8 years. It seems apparent that neither the age of the individual not the chronicity of the ulcer are important factors in the production of the bleeding episode.

Severity of Hemorrhage. While appreciating the difficulties in determining the severity of the hemorrhage, it seemed that the lowest red blood cell count was the best available measure. Consequently cases were grouped in 5 classes depending on the degree of anemia as determined by the lowest red blood cell count. Twenty-six per cent of the cases had a lowest red blood cell count between 1 and 2 million, 33% between 2 and 3 million, 25% between 3 and 4 million, 13% between 4 and 5 million and 3% above 5 million. The large proportion of severe hemorrhages is in accordance with the fact that only those cases were considered which had had a definite episode of hematemesis or melena. The severity of the hemorrhage appeared to be quite independent of the age or sex of the individual or the duration of symptoms of the ulcer.

Duration of Hemorrhage. In describing the bleeding episode, the duration of the hemorrhage is of importance. However, no attempt has been made to study that in the present paper since it is not possible to determine it accurately. Even in cases of hematemesis

it seems a somewhat unwarranted assumption to postulate an abrupt onset of hemorrhage, while in cases of melena the onset may clearly have been insidious. As for the cessation of bleeding, Hesser's work[7a] indicates that this precedes the disappearance of occult blood from the stools by many days in a considerable number of cases.

Treatment. The great majority of the cases in this series (172 cases) were treated medically on a regimen approximating that proposed by Sippy[16a,b]*. Thirty-six cases, chiefly in the early years of the hospital, were treated on a soft solid diet without alkali, and 29 cases were operated on during their hospital stay.

Previous Hemorrhages. Sixty-eight cases (28%) had had one or more previous hemorrhages, 43 cases had had one earlier bleeding episode, 13 cases had had two, and an equal number three or more. Age appeared to have no relation to the number of previous hemorrhages.

Dietary histories were not sufficiently specific to permit a detailed analysis of diet as a factor in the problem of repeated hemorrhage.

Recurrences. There were 5 cases with a recurrence of bleeding sufficient to give either hematemesis or melena during the hospital stay. One of these was a case of definite perforation, well walled-off, 3 were deeply penetrating ulcers, and the last, a gastro-jejunal ulcer. Recurrence of massive hemorrhage under treatment thus is seen to be rare, and when it does occur, should suggest the possibility of penetration or perforation.

Convalescence. Barring continued hemorrhage or other untoward complications, which are rare, the subsequent course of these patients is determined by two main factors: 1, the control of the symptoms of the ulcer; and 2, the control of the symptoms of the anemia, which after the acute phase is dependent principally on the rapidity of the hematopoiesis.

It has been demonstrated that the Sippy régime, conscientiously followed, is highly efficient in controlling the symptoms of uncomplicated peptic ulcer.[4] As far as could be determined from the record, this régime was equally efficient in controlling symptoms of pain, nausea, bitter eructations and epigastric distress in patients who had bled recently.

The second factor in the course of these patients is the regeneration of the blood lost by the hemorrhage. Because it has been suggested that the alkali régime fails to promote as rapid regeneration as other methods of treatment,[10] an analysis of the rate of erythropoiesis was made in these cases.

* Bleeding peptic ulcer has been treated routinely by alkali therapy since 1918. The majority were treated as follows: In the first 24 hours an initial dose of MgO followed by $CaCO_3$ 2 gm. every ½ hour for 10 hours; in the second 24 hours $CaCO_3$ 1.3 gm. every ½ hour during the day and 2.6 gm. every hour at night if patient is awake; in the third 24 hours 30 cc. of milk and cream every hour with Sippy powder No. 2 every ½ hour. Thereafter the progressive Sippy régime is followed as usual without aspirations.

In the course of the hospital's history three standard methods of hemoglobin determination have been used at various times; Talqvist, Dare and Sahli. Because of the difficulty in comparing values obtained by three different methods it was considered impracticable to evaluate the rate of hemoglobin regeneration, and attention was concentrated on erythropoiesis.

Following the method of Schiødt[15b] the erythropoiesis was expressed as the average daily increment calculated week by week from the date of the lowest red blood cell count. This was done for 177 cases in which such data were available. Transfused cases were separately considered. Cases were grouped on the basis of the lowest red blood cell count, 25% being in the group between 1 and 2 million (average lowest red blood cell count 1.6 million), 40% in the 2 to 3 million group (average lowest red blood cell count 2.7 million) and 28% in the 3 to 4 million group (average lowest red blood cell count 3.4 million). The remaining 7% had lowest red blood cell counts greater than 4 million.

Table 1 shows the average daily erythropoiesis week by week for each of the three principal groups.

TABLE 1.—AVERAGE DAILY ERYTHROPOIESIS.*

	1st week.		2d week.		3d week.		4th week.		5th week.		6th week.	
	No. cases.	RBC rise.	No. cases.	RBC rise.	No. cases.	RBC rise.	No. cases.	RBC rise.	No. cases.	RBC rise.	No. cases.	RBC rise.
1 to 2 million	45	115.0	42	60.5	39	53.9	30	73.0	21	35.8	8	69.5
2 to 3 million	71	80.5	61	36.6	51	37.4	27	57.4	12	24.4	5	50.7
3 to 4 million	49	67.0	35	36.8	20	9.5	11	46.2	5	9.4		

* RBC rise represents the average daily increment in thousands of RBC/mm³. The consistent rise in the average daily increment present in the fourth week seems probably valid according to statistical criteria. Attempts to relate it to iron therapy, change in diet and length of hospital stay failed to show any significant degree of correlation. It also appears to be independent of age and sex.

It is apparent, on comparing the figures for the three groups, that the greater the anemia, the greater the average daily increment of red blood cells. The relation of the erythropoietic response of the body to the degree of anemia is shown even more strikingly in Figure 1. In an effort to determine whether such cases responded in a constant way to an anemia of a given degree regardless of the initial severity of the hemorrhage, the average weekly red blood cell counts for the 1 to 2 million group, beginning with the lowest average count, were plotted on the ordinate axis and the time interval on the abscissa. Having established this curve, the values for the weekly red blood cell counts of the 2 to 3 million group were plotted in such a way that the beginning of the curve (average lowest count) was placed on the curve of the 1 to 2 million group and a similar procedure was followed for the 3 to 4 million group. A graph was thus obtained with a single ordinate axis and multiple abscissal ones.

When this procedure was followed the three curves were found to coincide throughout their significant lengths.

It is, therefore, apparent from this figure that the erythropoietic response of the body is determined by the degree of the anemia at the moment and is independent of the initial severity of the hemorrhage itself. It also appears that though the rate of rise of red blood cells is greater in severe than in mild anemias, nevertheless it takes somewhat longer for patients with a severe initial anemia to attain an essentially normal red blood cell count than for those with a mild one. This is not strictly in accord with the hypothesis advanced

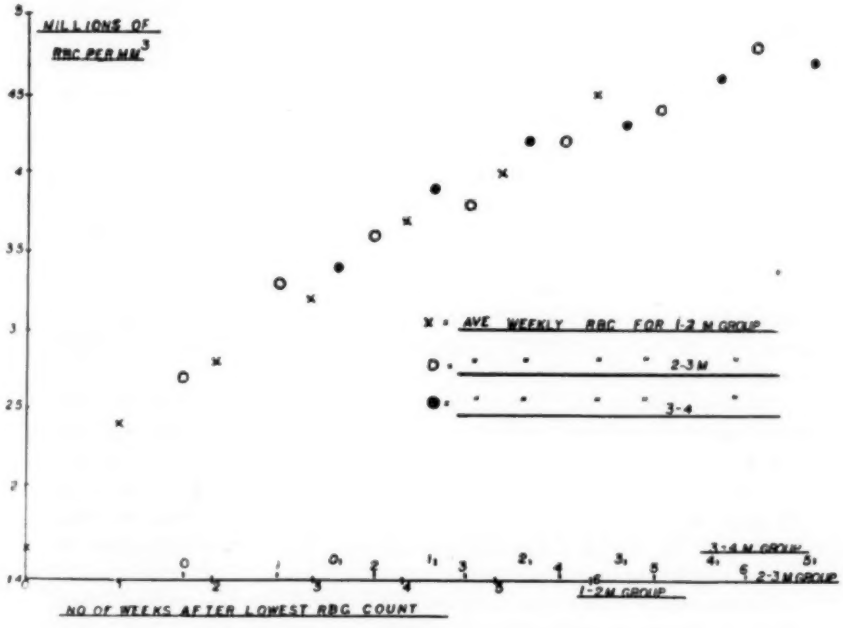

FIG. 1.

by Schiødt,[15b] that, regardless of the initial degree of the anemia, the red blood cell counts of all cases following hemorrhage "tend to meet in one point, 4.54 million, 33 days after the lowest erythrocyte value was measured." Figure 1 indicates that the cases with the lowest red blood cell counts between 3 and 4 million might in general be expected to attain a normal red blood cell count 3.5 weeks sooner than those in the 1 to 2 million group and 1.5 weeks sooner than those in the 2 to 3 million group.

The rate of erythropoiesis was found to be slightly, but not significantly lower, in the patients over 40 than in the younger group. There was not a sufficiently large number of female cases to permit

a significant correlation of erythropoietic rate with sex though the males seemed to show a tendency to a more rapid rate of regeneration.

In an attempt to evaluate the importance of diet in the erythropoiesis of these cases, both the dietary history before and the dietary treatment after the hemorrhage were considered. Patients whose diets before hemorrhage were the equivalent of, or in a few cases less liberal than, the strict 4th week Sippy regimen showed an average erythropoiesis fully as good as those who had been on a more liberal regimen. It would appear that the 4th week Sippy regimen is as liberal as necessary for satisfactory blood regeneration in the usual case of bleeding ulcer.

Since the majority of these cases were treated by the progressive Sippy regimen, an effort was made to evaluate the relative erythropoietic effect of the first and fourth week diets. This was impossible in the early weeks of treatment because of the small number of cases on fourth week diets during this period and in the later weeks because of the small number of first week diets. In the third week after the lowest count approximately the same number of cases (45 and 58) were treated by each of the two regimens, and the erythropoiesis for that week was essentially the same for the two groups.

This result is not unexpected. It is true that the first week Sippy regimen is a vitamin deficient diet, and if adhered to for a sufficiently long time, might result in anemia. It would hardly be expected, however, that in as short a period as 3 to 4 weeks such a diet could result in retarded erythropoiesis.

Recent reports by Danish investigators[15a,c] have indicated the superior erythropoietic effect of a liberal "purée diet" throughout the course of treatment of bleeding ulcers over more restricted dietary regimens. Rates of erythropoiesis were available in only 20 cases in the present series treated throughout their hospital stay by a liberal, bland diet without alkali. These cases showed no better erythropoiesis than the group as a whole.

The average daily rise in blood cell count for the entire group (Fig. 1) was compared with the figures reported by Schiødt[15c] for a group of patients treated by "purée diet" with iron. The values for Schiødt's group were found to be essentially the same as the comparable values in Figure 1.

When the rate of erythropoiesis for the weeks during which cases were given iron therapy by mouth* was compared with the average erythropoietic rate for the group as a whole, no better values were found. In these cases of acute blood loss the administration of iron did not seem to affect the rate of erythropoiesis. It should be emphasized again that no studies were made on the rate of hemoglobin regeneration.

A total of 24 cases received one or more blood transfusions while in the hospital. The erythropoiesis of 17 of these was studied. It

* Usually 2 to 3 gm. of ferric ammonium citrate daily.

was found that the rise in red blood cell counts during the first week after transfusion was on the average 300,000 RBC greater than the corresponding values in Figure 1 in the 1 to 2 and 2 to 3 million groups. After this initial rise the hematopoiesis proceeded at the usual rate depending on the degree of anemia present at that time; the transfusion appeared to exert neither a stimulating nor a depressing effect on the bone marrow. From this it would appear that, when a purely elective transfusion is to be considered for the purpose of speeding recovery, the best effect will be obtained if it is given after the red blood cell count has reached a level of about 3.5 million. Under such circumstances Figure 1 indicates that a transfusion of 500 cc. of whole blood should enable an average patient to attain a normal red blood cell count nearly a week earlier than otherwise. The same transfusion in the presence of a more severe anemia would produce far less proportionate effect due to the higher rate of erythropoiesis at that time (see Fig. 1).

Prognosis. Previous studies in the literature have been directed usually at the mortality rate and immediate treatment of the acute emergency rather than at the subsequent course of the patients who survive the bleeding episode. The essential criterion of recovery from such an episode is the restoration of a normal blood level. Figure 1 enables one to estimate the length of time necessary for this process in the average case as reckoned from the lowest red blood cell count. It is of interest to note that in 44% of the surviving patients the lowest red blood cell count was on entry and that it occurred within 1 week after entry in another 34%. Only 13 patients failed to reach their lowest red blood cell count within 2 weeks after entry, and of these only 3 had lowest red blood cell counts below 2 million. The other patients who failed to reach their lowest red blood cell count for an equally long period of time and who also showed occult blood in the stools, did not reach such a critical anemia despite their long continued bleeding.

Once the patient has reached his lowest red blood cell count his recovery time appears to depend on the degree of the anemia as noted above. On the average, if the lowest red blood cell count is between 1 and 2 million it should require a little over 6 weeks to attain a red blood cell count of 4.5 million. If the lowest red blood cell count is between 2 and 3 million, it should require above 5 weeks, and if it is between 3 and 4 million, about 3 weeks. Should the rate of recovery in an individual case lag much behind the average, some complication might well be suspected.

Mortality. The efficacy of the treatment of the acute episode of bleeding usually is assessed in terms of mortality. In the present series 20 patients died. In 10 of these hemorrhage was considered to be the principal cause of death, and it contributed directly to the death in 3 others, a net mortality of 5.5%. In the 7 remaining cases the hemorrhage was not directly contributory to death; 1 died of

cerebral hemorrhage after the red blood cell count had returned to normal, 1 died of a transfusion with incompatible blood and 1 of dehydration, uremia and pneumonia without appreciable anemia. There were 5 postoperative deaths, but only 1 of these had a severe preoperative anemia (1.7 million); the other 4 did not (3 to 5 million). Only 4 cases died within 48 hours after the presumed onset of the hemorrhage, 3 died within the first week after the onset and the remainder at longer intervals. Of the 13 cases in which anemia contributed significantly to death, the median age was between 60 to 65 years and the youngest was 54 years as compared with a median age of 45 years for the entire series, which is essentially in accord with the figures for other series.[3,5,7b,11] It appears that young individuals with bleeding ulcers rarely die, and when they do, it is usually as a result of complications, rather than exsanguination. It also seems that in this series death from exsanguination was not, as a rule, sudden even in old people but occurred only after several days of continued bleeding. The literature varies on this point.[8a,13a]

It appears that judged by the criterion of mortality also, the Sippy regimen is a satisfactory method of treatment for bleeding peptic ulcer. Though lower mortality rates have been reported,[6,9,13a,b,14] the figure of 5.5% compares favorably with the mortality in most similar series.[1,2,5,12,17]

TABLE 2.—MORTALITY IN BLEEDING PEPTIC ULCER.

Name.	No. of cases.	Mortality rate (%).
Aitken	255	11.0
Bulmer	467	9.9
Goldman	349	11.1
Gram	106	2.0
Hurst and Ryle	82*	4.8
	258†	1.6
Lahey	346	5.0
Meulengracht	368	1.3
Umber	433	9.5

* Guy's Hospital cases.
† Private practice.

Each of the series in Table 2 consists of patients with gross hematemesis or melena. However, the percentage of proven ulcer in any of the groups in which it could be determined was far below 86%, the figure for the present series. The extent and the direction to which the inclusion of cases of hematemesis or melena not resulting from peptic ulcer has influenced the mortality statistics in these series seems difficult to determine.

Contrary to statements[2,3,11] that the mortality in males is appreciably greater than in females, there appears no significant difference between the sexes in this series; 2 of 46 females and 11 of 184 males died as a result of hemorrhage.

Opinion has differed also regarding the prognosis of bleeding ulcer in patients with a history of previous hemorrhage. In this series the mortality in patients with previous hemorrhage does not differ significantly from that for the group as a whole.

Summary. 1. Records of 237 cases of bleeding peptic ulcer have been analyzed with special reference to symptomatology, the anemia produced by the hemorrhage and the subsequent course of the patient.

2. Over one-third of the patients noted symptoms of weakness, syncope or dyspnea before any external evidence of bleeding. Evidence of exacerbation of the activity of the ulcer prior to the bleeding was found in only 28% of the cases.

3. Approximately one-fourth of the patients in each decade had had ulcer symptoms for less than 1 year and over 8 years respectively before the hemorrhage.

4. Severity of hemorrhage appeared quite independent of the age and sex of the individual.

5. Age appeared to have no relation to the number of previous hemorrhages.

6. The weekly rate of erythropoiesis was determined for 177 cases on the basis of the lowest red blood cell count. The rate of erythropoiesis appeared strictly dependent on the degree of anemia present at the time, regardless of the duration of the illness and the initial severity of the anemia.

7. The observed erythropoietic rate for cases in this series, the large majority of which were treated on a Sippy regimen, was fully as good as that reported for patients treated with a liberal, "puréed diet" and iron.

8. Beyond the actual increment of donated cells transfusion appears to have no effect on the rate of erythropoiesis.

9. A net mortality of 5.5% was present for the series. This appeared to be independent of sex or number of previous hemorrhages.

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CYSTEINE HYDROCHLORIDE AS AN ANTICOAGULANT FOR CLINICAL USE.*

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The Conditions Produced by Increased Coagulability of the Blood. Much study has been devoted to the hemorrhagic diseases, but the disorders resulting from an excessive tendency of the blood to coagulate have received little attention. Such conditions unquestionably exist. Thrombosis of blood in normal vessels has been demonstrated experimentally by Flexner,[4] Mills,[13] and others, following injection of foreign protein and organ extracts, by Kusama[9] following injection of a variety of substances, by Stuber and Lang[23] following exposure to carbon dioxide, by Meyer[12] following exposure to carbon monoxide, and by many other investigators using other means. Common examples of clinical states in which thrombosis occurs in apparently normal vessels are the thrombophlebitis occurring in pregnancy, and after surgical operations, "spontaneous" thrombosis of the retinal vein in young subjects, thrombophilia,[17] and polycythemia. Evidence has recently been adduced[19a] which suggests that multiple sclerosis and certain forms of "encephalitis" (for example, the postinfectious type) are the result of thrombosis of small cerebral vessels, and it was this aspect of the problem which called it to our attention. There are doubtless other diseases which could be added to the list.

The conception of thrombosis in *normal* vessels as a result of a disorder of the blood plasma has not been easily accepted. Prior to Virchow's time, injury to the vessel wall was generally held to be an essential first step in thrombosis. Modern pathologists recognize that clotting may occur in normal vessels. Aschoff[1] for example, says: ". . . . Thrombosis is the function of a number of variables. . . . . Among these may be mentioned here, first, changes in the blood plasma (diminished or increased coagulability), secondly, changes in the blood elements (increased or decreased powers of agglutination), thirdly, changes in the blood flow (slowing and formation of eddies), and lastly, changes in the vessel wall itself (endothelial damage). An enquiry into the mechanism of thrombosis

* The expenses of this investigation were defrayed by a grant from Child Neurology Research (Friedsam Foundation). The cysteine hydrochloride was kindly supplied by Merck & Co.

shows that sometimes one factor, sometimes another plays the principal rôle . . . . The existence of . . . . increased coagulability, and the likelihood that it is a promoting factor, or better, an accompanying phenomenon, cannot be denied. . . . . We do not know as yet anything of the phenomena which precede agglutination of platelets, and which are the very earliest factors in thrombosis . . . . I can find in the literature no well-authenticated cases in which thrombosis has really been brought about by changes in the endothelium, a factor which is regarded by many authors as of special importance."

Since the above statement was written, a good start has been made toward learning more about the stability of the plasma under various circumstances.[10]

Previous Attempts to Decrease the Coagulability of Circulating Blood. A number of substances have been used to prevent coagulation of circulating blood in animal experiments. Outstanding among these are hirudin[5] and heparin.[8] Pickering and Hemingway[18] succeeded in preventing thrombosis even at the point of contact with a foreign body by administration of heparin. Peroral administration of citric acid was reported by Brooks and Crowell[2] to reduce artificially produced thrombi. Marris[11] saw arrest of thrombosis in patients after repeated intravenous injection of sodium citrate, but others[3] have employed citrates to promote coagulation. Sodium thiosulphate has been recommended for the treatment of thrombophlebitis and thrombangiitis obliterans,[21] but evidence of its effectiveness is not clear. More recently, Murray and Best[16] and others[6] have suggested the use of a more potent heparin by intravenous drip. The effect of the heparin may apparently be made as powerful as is desired, as Murray and Best have shown (loc. cit.), but it lasts only 4 hours after a single dose. Long continued use might become dangerous because repetition of an injection before the effect of the first dose has worn off might cause serious or even fatal bleeding. Therefore, heparin may be of use in the prevention of postoperative thrombosis, but it could not be employed over long periods of time in the conditions characterized by a chronic lability of the plasma. As it was exactly such conditions for which a treatment was sought, a search was instituted for an anticoagulant effective when given by mouth.

Previous Observations on the Anticoagulant Activity of Cysteine Hydrochloride. In a search for some substance which might be used clinically as an anticoagulant over long periods of time, our attention was attracted by the paper by Sterner and Medes[22] on cysteine hydrochloride. The anticoagulant effect of this substance was first observed, entirely by chance, by Mueller and Sturgis in 1932.[15] They were using it as one of a series of growth-promoting sulphur-containing substances, and noticed that it inhibited the clotting of plasma used as a medium. Sterner and Medes studied its action in more detail, and found that it acted as an antiprothrom-

bin. They state that it prolongs both the bleeding time and the clotting time, whether injected intravenously or administered by mouth. The graph which is presented shows a prolongation of bleeding time from 4 to 6 minutes, but does not demonstrate a prolongation of clotting time, using "the 8 mm. tube method." In *in vitro* experiments, a marked prolongation of clotting time (from less than 10 minutes to 50 minutes) occurred with molar concentrations of 0.16 to 0.64 of cysteine. Methionine, taurine, and taurocholic acid exhibited somewhat similar properties.

In recent experiments on the production of "encephalitic" lesions by intravenous injection of coagulants, we found that cysteine hydrochloride given intravenously or by mouth would prevent death from several times the usual lethal dose of a well-standardized lung extract.[7] It was an obvious step, therefore, to test its effects further in animals and in human beings.

Methods. The following technique for determination of blood coagulation was finally worked out as the most dependable one, after a number of other methods had been tried and discarded: a series of 15 test tubes 8 by 75 mm. was set up in a wire rack and approximately 1 cc. of blood was put into each. The technique was rigidly standardized. Special care was taken to clean the syringes and test tubes in a uniform fashion, and only new 18-gauge needles were employed. Any determinations in which there was a delay in securing blood were discarded, as were those in which bubbles appeared in the syringe or tube. Blood was taken by cardiac puncture in unanesthetized dogs, and from the arm-veins of patients who were specially chosen as permitting sure and easy venipuncture. The determinations were carried out in rooms maintained at a temperature between 25° and 30° C. At certain intervals, usually of 10 to 20 minutes at the beginning, closer toward the end of the observation, one tube was inverted and its content poured out. The time at which the first signs of a clot were observed and also that at which the entire content of one tube was clotted, so that no liquid blood could be poured out even by jerking the tube, were recorded. In a series of experiments the times were charted for the appearance of the first clot, and those at which approximately one-half, three-quarters and the whole amount of blood were clotted. (Figure 3 shows one of these observations carried out over 10 days with 7 determinations during this period.) Each of the 15 specimens is handled only once. A liquid residual of blood poured into another tube usually clots within a few minutes, while untouched specimens will remain partly liquid for a considerable length of time. Care was taken to discard specimens in which sedimentation had occurred. Sanguinolent serum after complete coagulation was easily distinguished from unclotted blood. Whenever one specimen was found completely clotted the following tube was examined until either all were found clotted or as occurred in some instances, one specimen was not quite clotted. In these cases, the observation was continued. No experiment was accepted until three consistent determinations had been secured before administration of the drug.

It is fully realized that the determination described above differs essentially from the one used routinely for the clinical observation of clotting time. This is defined for instance in the Thorndike Laboratory[14] as the time after which a surface clot has formed thick enough

to hold the amount of 2 cc. of blood in a tube of certain dimensions when the tube is inverted. When this method is used the normal clotting time is 12 minutes for specimens kept at 37° C. in a thermostat. This might correspond to the "first clot" stage in our determination (Fig. 1*a*).

The reason for abandoning this or some similar arbitrary endpoint was the following: In tubes of the size used in our experiments, the first clot is as often as not a layer adherent to the glass. This slowly becomes thicker and at some later time usually the surface layer coagulates. It is then still possible by shaking the tube to

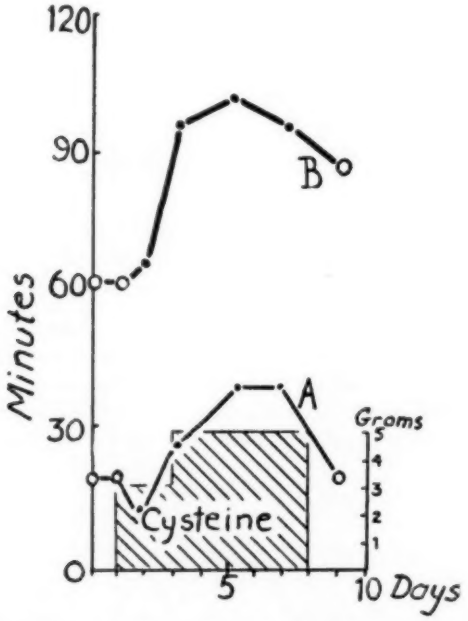

FIG. 1.—Prolongation of coagulation time of Patient H. during 8 days of treatment with cysteine hydrochloride by mouth. Curve *A*, first clot. Curve *B*, completely clotted. Note persistence of effect for a day after discontinuance of the drug.

obtain blood which is still liquid but will clot promptly in another tube. The determination of the time for complete coagulation appeared to be more consistent than that required for the appearance of the first signs of clot. It is marked by the moment when retraction begins and serum is squeezed out. Figures were consistently obtained which were much higher than those usually given. Thus, coagulation times up to 60 minutes in normal dogs and up to 105 minutes in man during a control period were observed, after the technique had been thoroughly systematized. The fact that observations were made at room temperature instead of at body temper-

ature accounts for part of the difference. It was also observed[20] that blood taken with a needle of a large gauge remains liquid much longer than blood taken with a small gauge needle.

Animal Experiments. Satisfactory experiments were carried out in 8 dogs. The dogs were trained to lie still for a cardiac puncture.

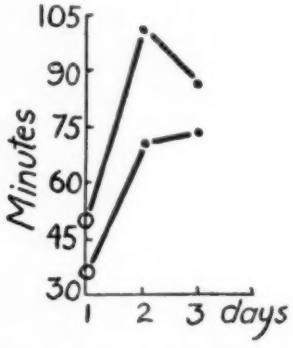

FIG. 2.—Coagulation times (in minutes) of 2 dogs, each of which received 5 gm. cysteine hydrochloride by stomach tube immediately after the first sample of blood was taken.

The cysteine was injected intracardially in doses of 0.2 gm. per kilo in 4 experiments. There was a subsequent rise of 40 to 100% in 3 of them, which reached its height in a few hours, and was still apparent 24 to 40 hours after injection. A typical curve is shown in Figure 3. Cysteine hydrochloride was given by stomach-tube in

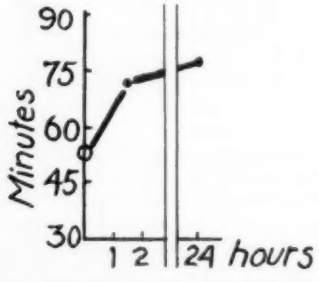

FIG. 3.—Coagulation times (in minutes) of a dog which was given 3 gm. cysteine hydrochloride intracardially immediately after the first sample of blood was taken.

8 other experiments, in doses of 0.4 to 0.75 gm. per kilo. Four of these experiments had to be discarded because of errors in technique; but in the remainder an increase of clotting time of 25 to 100% was obtained, which in several instances lasted for 48 hours after the injection (Fig. 2).

Observations on Patients. All of the patients studied suffered from multiple sclerosis. They were chosen both as having the disease in a relapsing form, and as satisfactory subjects for venipuncture.

FIG. 4.—Alterations in the clotting time of Patient W.D.N. over a period of 12 weeks on cysteine hydrochloride by mouth.

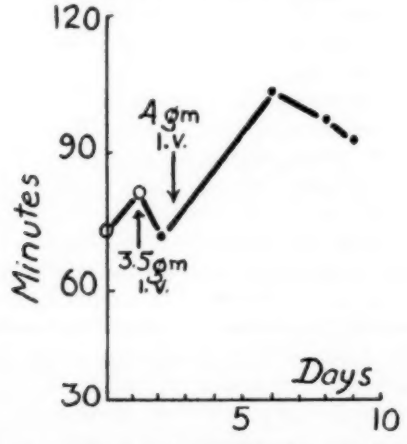

FIG. 5.—Alterations in coagulation time produced by 2 intravenous injections of cysteine hydrochloride in saline, 4 days apart (Patient M.).

After three or more control observations a day or two apart, administration of cysteine was begun. In 6 instances, cysteine was administered intravenously in 10% solution in normal saline. In 17 other cases, it was given by mouth, in large capsules, at a dosage of 3 to

5 gm. daily. When given in larger doses, gastric distress and malodorous eructations often occurred. One patient developed an extensive area of ecchymosis on her right calf with some ecchymotic spots on her left leg as well. This occurred after 11 days of intensive treatment. Platelets had been reported normal previous to the administration of the drug and since there was no history of bruising easily, it was assumed that this was probably due to the action of cysteine. A repeated platelet count showed 400,000 platelets per c.mm. and a bleeding time of 3½ minutes. Two patients complained of an increased menstrual flow, which recurred each month during the course of treatment. The drug was otherwise well borne.

In 17 out of these 23 instances, an increase in coagulation time was observed. The rise varied from 30 to 90%. Typical records are seen in Figures 1, 4 and 5. In several instances, there was a delay of 1 or 2 days before the increase occurred.

The patients mentioned are not the only ones who have taken large amounts of cysteine. Seven other patients suffering from multiple sclerosis have taken similar doses by mouth daily for periods varying from 6 months to over 2 years, with no untoward symptoms. In this group, studies of coagulation could not be carried out.

Therapeutic Results. The period of observation is too brief and the series too small to permit evaluation of therapeutic results. Obviously, treatment with an anticoagulant should not be expected to improve the symptoms of multiple sclerosis,[19b] nor are relapses entirely prevented by the amount of the drug which can be given. Pending the development of more powerful and dependable anticoagulants of prolonged action, however, it seems worth while to continue the observations.

Other Possible Indications for Treatment With Cysteine. There may be a question whether cysteine is a sufficiently active anticoagulant to prevent postoperative thrombosis. It appears to be harmless in moderate doses, however, and is comparatively inexpensive. It might be even more advantageous in the treatment of established thrombosis, to diminish the likelihood of extension.

There are other conditions in which an anticoagulant which is effective when given by mouth might be useful, for example, cerebral or coronary thrombosis, phlebitis migrans, and subacute bacterial endocarditis. We have used it in one case of the latter condition, but in such an advanced stage that its failure to modify the process is difficult to evaluate. An extensive thrombosis of the femoral vein complicating lead encephalitis in a child of 18 months was arrested following its use.

Summary. 1. The intracardial injection of cysteine hydrochloride in dogs was followed by a rise in coagulation time of 40 to 100% in 3 out of 5 experiments.

2. The administration of cysteine hydrochloride to dogs by stomach tube was followed by an increase of clotting time of 25 to 100% in all technically satisfactory experiments.

3. Cysteine hydrochloride was also administered by mouth to 23 patients in whom the diagnosis of multiple sclerosis had been made. In 17, a rise of coagulation time was observed, which varied from 30 to 90%.

4. Cysteine hydrochloride is well tolerated by most patients in doses up to 3 gm. per day, over many months. No serious symptoms have been observed to follow its use.

5. It is therefore suggested as an anticogulant of rather low efficiency for use over long periods of time, for conditions in which such an agent might be valuable.

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A STUDY OF THE CLOTTING DEFECT IN HEMOPHILIA: THE DELAYED FORMATION OF THROMBIN.*

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No very general agreement exists concerning the nature of the clotting defect in hemophilia. The literature of this subject has been reviewed by Wöhlisch,[11] and more recently in the papers of Patek and his associates.[7,8] Practically all workers agree that the plasma fibrinogen is essentially normal in amount and reactivity, and that no excess of antithrombin is present. Our results substantiate these views. It follows, by exclusion, that the defect lies

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in one or more of the factors concerned in the formation of thrombin. However, no quantitative studies have been made on the speed with which prothrombin is converted into thrombin in hemophilic blood. To follow this reaction we have developed an accurate method for the measurement of the prothrombin conversion rate. Using the prothrombin titration technique devised in this laboratory,[9,10a] the residual prothrombin content of the plasma (or serum) is determined at intervals, beginning shortly after the blood is drawn and continuing until the prothrombin supply is practically exhausted a number of hours later.

The experiments which follow show that in hemophilia the prothrombin conversion rate is extremely slow throughout the entire period of observation. It is also shown that the conversion rate is brought to normal by adding an extremely minute amount of a thromboplastic organ extract. If given time, the formed elements of the hemophilic blood also liberate materials sufficient to accomplish the same result.

Experimental Observations. Five cases of hemophilia were studied. Most of the data presented were from 1 patient who was available for continuous study over a period of about 7 months, but practically all of the experiments were repeated on one or more of the other patients.

In all 5 cases the prothrombin content of the plasma, determined by the method of Warner, Brinkhous and Smith,[9,10a] was within the limits of normal. The highest value was 110% of the normal control, the lowest value 90%. The fibrinogen content of the plasmas, determined by the method of Jones and Smith,[5] was within the normal range of 340 to 400 mg. per 100 cc.

Tests for antithrombic activity also gave normal values. Both plasma and serum, incubated with thrombin solutions, destroyed thrombin in the same amounts and at the same rates as did the normal controls. Also, thrombin solutions clotted hemophilic plasma with the same rapidity as they clotted normal plasma. This confirms previous observations of other workers and serves to show that the fibrinogen of hemophilic plasma is normally reactive.

The Slow Conversion of Prothrombin Into Thrombin in Hemophilia. Chart 1 shows the very slow rate at which prothrombin is converted into thrombin in hemophilic blood. In this experiment, the hemophilic blood was first allowed to stand for 15 minutes at 28° C. to permit, as nearly as possible, a standard amount of disintegration of platelets and blood cells. Cell-free plasma was then obtained by centrifugalization (4000 r.p.m. for 15 minutes). At this time the prothrombin content of the plasma was still essentially the same as that of the oxalated control plasma from the same individual, showing that in 30 minutes no detectable amount of prothrombin had been converted. This is in accord with the fact

PROTHROMBIN IN PER CENT

that the plasma did not clot until another 60 minutes had elapsed. Following clotting, the prothrombin titer fell extremely slowly. After standing 24 hours, 50% of the prothrombin still remained unconverted, and to convert 90% of the prothrombin a total period of 3 days was required.

The normal control blood in this experiment was treated in the same manner as given above. It clotted, however, in 10 minutes, so that on centrifugalization, serum was obtained instead of plasma.

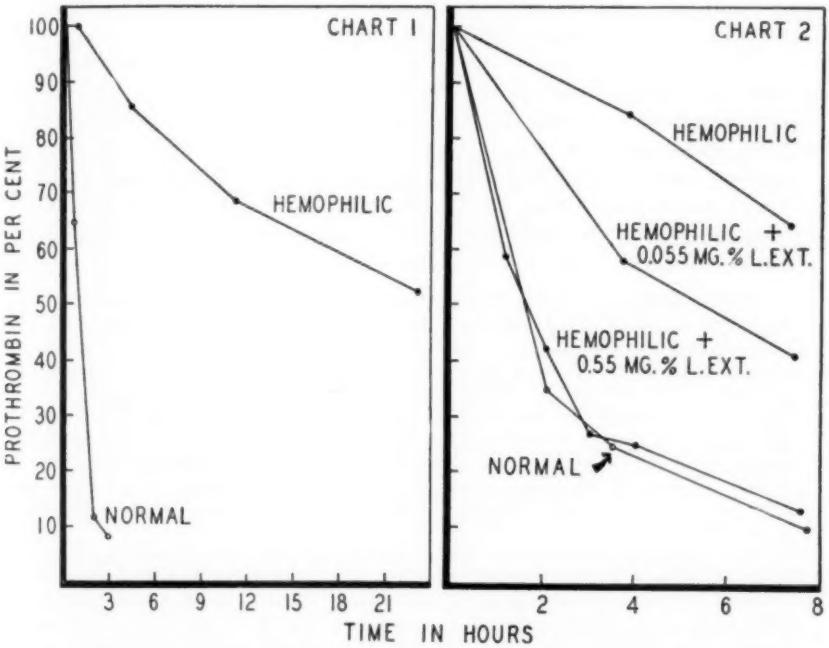

CHART 1.—The blood in each case was allowed to stand for 15 minutes. It was then centrifugalized for 15 minutes at 4000 r.p.m. The residual prothrombin content of the serum (or plasma), determined at intervals, is expressed in per cent, using its oxalated control plasma as 100%. The blood was kept at 28° C. throughout the course of the experiment.

CHART 2.—Each blood sample was centrifugalized immediately, after which the residual prothrombin content of the serum (or plasma) was determined at intervals.

The serum, analyzed immediately, had already lost 35% of its prothrombin within this 30-minute period, and within 3 hours over 90% of the prothrombin had been converted.

By comparing the prothrombin conversion rates at a given level of prothrombin, it is evident that the amount converted in unit time is fully 30 times as great in the normal as in the hemophilic serum. This slow formation of thrombin in hemophilia allows the thrombin to be destroyed by antithrombin almost as rapidly as it is

formed. At no time did the serum contain more than the merest trace of thrombin, and on adding fibrinogen many minutes would elapse before a clot would form. In normal serum, on the other hand, the thrombin titer is such that a clot typically forms in 10 to 60 seconds.

Associated with the low thrombin titer in hemophilic blood is the great length of time required for the complete clotting of its fibrinogen. After the onset of clotting, successive crops of fibrin appear over a period of 1 to 2 hours or even longer. In contrast to this slow clotting, only a very few minutes are required for the complete conversion of fibrinogen into fibrin in normal blood.

The Effect of Thromboplastin Upon the Prothrombin Conversion Rate in Hemophilia. It is known that organ extracts, rich in thromboplastin, accelerate the clotting of hemophilic blood. We have undertaken to test in a quantitative way the effect of such extracts upon the prothrombin conversion rate. The experiments which follow show that the conversion rate in hemophilia can be brought within the normal range by adding to 100 cc. hemophilic blood less than 1 mg. of the material extracted from lung.

One hundred grams of ground beef lung were extracted for 48 hours at 5° with 100 cc. saline (0.9% NaCl). The extract, obtained by centrifugalization, was neutralized (pH 7.4). It contained 3.3 gm. % total organic solids. One portion of the extract was diluted 1000 times with saline; another portion 10,000 times. To 0.2 cc. of each was added 1 cc. freshly drawn hemophilic blood. The first tube, containing 0.55 mg. % extracted material, clotted in 9 minutes; the second, containing 0.055 mg. % extracted material, clotted in 21 minutes. One control tube was prepared by mixing 0.2 cc. saline with 1 cc. hemophilic blood; another by mixing 0.2 cc. saline with 1 cc. normal blood. The hemophilic clotted in 55 minutes; the normal in 10 minutes.

Four mixtures, duplicates of the 4 above, were then prepared and centrifugalized immediately (4000 r.p.m. for 15 minutes at 5°). The plasma (or serum) was then removed and allowed to stand 8 hours at 28°. The residual prothrombin content of each mixture was determined at intervals during this period. The prothrombin conversion curves are given in Chart 2.

In this experiment an effort was made to reduce the breakdown of cells and platelets by immediate centrifugalization of the blood samples at a low temperature. This had little effect on the hemophilic specimen, for the prothrombin conversion rate (Chart 2) was approximately the same as that shown in Chart 1. In the normal blood these precautions were rather effective, however, for the prothrombin conversion rate was less rapid than in the previous experiment. The disintegration of blood cells and platelets which occurred here probably did not exceed that of the normal blood during its 10-minute clotting period. Nevertheless, the conversion was still relatively rapid: at comparable levels of prothrombin it was almost 10 times as rapid as in the hemophilic blood.

The effect of adding small amounts of lung extract is also shown

in Chart 2. It will be noted that addition of less than 1 mg. extracted material per 100 cc. hemophilic blood is sufficient to restore the prothrombin conversion rate to normal. Addition of less than 0.1 mg. per 100 cc. has a definite, but less pronounced, effect.

The striking effect of such minute amounts of lung extract is all the more remarkable when one reflects that the product is a crude mixture containing much inert material. It is a reasonable assumption that the active principle in the extract is thromboplastin, for it is known that saline extracts of lung have great thromboplastic power. One cannot exclude the possibility that they may also supply important clotting factors other than thromboplastin, but there is as yet no evidence that this is so.

The effect of adding large amounts of lung extract was studied also. Under these circumstances the prothrombin is converted very rapidly into thrombin, and the prothrombin conversion rates, both normal and hemophilic, are identical. If the undiluted lung extract is added to an equal volume of normal and of hemophilic plasma, 85 to 90% of the prothrombin is converted in 50 to 55 seconds after recalcification in each case.

A similar result is obtained when one treats diluted plasma with an excess of thromboplastin. In the titration of prothrombin, the plasma is diluted routinely to a prothrombin concentration of 1 unit. In the presence of lung extract and calcium, there is complete conversion of the prothrombin in hemophilic plasma in 4 minutes, exactly as in the normal control plasma.

It has been suggested[1,2] that the prothrombin in hemophilia is relatively unreactive and hence is responsible for the clotting defect. With the methods used in the experiments just cited, we have already shown that the prothrombin of human plasma is less reactive than that of many other species.[10b] This slow convertibility in man is a handicap in the control of hemorrhage, but the present experiments would indicate that in hemophilia this handicap is no greater than it is normally.

The Formed Elements of the Blood in Hemophilia: Their Effect on the Prothrombin Conversion Rate. That hemophilic platelets contain a thrombin-forming factor, analogous to that of our lung extract, has been shown by many workers. The experiments of Opitz and Zweig[6] are especially significant. They allowed citrated hemophilic blood to stand in contact with its cells and platelets. When recalcified 12 to 24 hours later, clotting occurred in a normal time. Platelet-free plasma, however, was not improved by standing. We have confirmed these findings, and have extended our observations to place this experiment on a quantitative basis.

The prothrombin conversion rates were determined in blood and in plasma which had been allowed to stand for 24 hours in citrate (Chart 3). The prothrombin conversion rate of the aged cell-free plasma was not affected by the incubation. It was practically

identical with the fresh hemophilic control, not shown in the chart. On the other hand, hemophilic plasma incubated in contact with the cells acquired the ability to form thrombin at practically the same speed as does normal plasma. This shows definitely that the cellular elements are concerned, and that, if given time, they liberate the thrombin-forming factor in amounts adequate for a normal rate of prothrombin conversion.

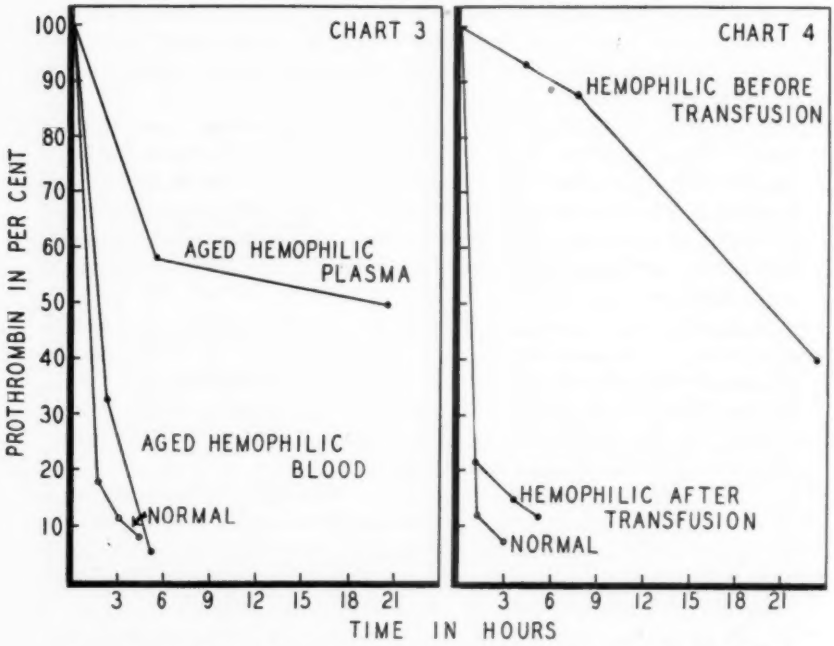

CHART 3.—Each blood sample was mixed with one-tenth its volume of 2.85% sodium citrate. The normal control plasma was recalcified immediately after centrifugalization. Its clotting time was 7 minutes. The residual prothrombin content of its serum was then determined at intervals. Hemophilic plasma, obtained at the same time, was allowed to stand 24 hours at 28° C. before recalcification. It clotted in 68 minutes. Its residual prothrombin was then determined at intervals (upper curve). The whole citrated hemophilic blood was allowed to stand 24 hours at 28° C. before centrifugalization. The plasma obtained at that time was immediately recalcified. Its clotting time was 10 minutes. The residual prothrombin content of the serum was determined at intervals (middle curve).

CHART 4.—The blood samples were treated as in Chart 1.

One theory of the clotting defect in hemophilia centers about defective platelet function. The evidence available indicates that the platelets contain a normal amount of thromboplastin, although it must be admitted that methods for assay of thromboplastin are highly inadequate. Morphologic studies of the platelets, on the

other hand, show that they are unduly stable.[4] This would indicate that their thromboplastin, although normal in amount, is liberated more slowly than in normal blood. In harmony with this view are our observations that approximately 24 hours are required for the release of sufficient thromboplastin to give normal clotting. It is significant that when normal blood is collected carefully to prevent undue destruction of cells and platelets, the prothrombin conversion is greatly lengthened (see Charts 1 and 2). This suggests that if normal blood were collected entirely free of formed elements and their distintegration products by the method of Fuchs,[3] it might be quite similar, if not identical, to the plasma of hemophilic patients. With such plasma as a control it might be possible to make a crucial test of the theories that the prothrombin is relatively unreactive or that its conversion is blocked by some inhibitor.

The Effect of Transfusion in Hemophilia. Blood transfusions remain one of the most successful means of controlling hemorrhage in hemophilia as well as of preparing these patients for operation. After transfusion, the clotting time often becomes normal and may remain so for many hours. We have had the opportunity of observing the effect of transfusion in several cases. One of these was given 300 cc. of normal blood in preparation for tooth extraction. Prior to transfusion the clotting time was 100 minutes; 12 hours afterwards it was 10 minutes. The prothrombin conversion rate, given in Chart 4, was quite slow before transfusion, but when tested 12 hours afterwards it was found to be normal.

One can postulate that normal plasma supplies some factor which hemophilic plasma lacks, but it is even more likely, in our opinion, that the cells and platelets of the donor's blood supply the missing element. A simple explanation is that the element so supplied is thromboplastin. This possibility needs further study, both because of its theoretical importance, and because of the therapeutic implications.

Summary. A quantitative study of changes in the prothrombin titer of hemophilic blood shows that its prothrombin is converted very slowly into thrombin. This delayed prothrombin conversion can be corrected by adding less than 1 mg. of crude thromboplastin to 100 cc. hemophilic blood. Evidence indicates that the prothrombin and fibrinogen are normal in amount and in reactivity in this disease. There is no excess of the antithrombin. Emphasis is placed upon the formed elements of the blood and the sluggishness with which they liberate thromboplastin.

The beneficial effects of transfusion in hemophilia were studied.

The writer is indebted to several members of the Departments of Pediatrics and of Internal Medicine, especially to Drs. R. L. Jackson, E. L. DeGowin, and O. D. Thatcher, for their generous coöperation throughout the course of this study.

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BLOOD STUDIES IN LYMPHOGRANULOMA VENEREUM; WITH SPECIAL REFERENCE TO SERUM PROTEINS.

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In the past decade the literature on various aspects of lymphogranuloma venereum has been accumulating rapidly. In the United States the first paper on the subject appeared in 1932.[2] However, in spite of the many phases of the disease which have been described and discussed, only two groups of authors have written concerning the derangement of serum proteins which usually occurs.

Williams and Gutman,[12] in 1936, were the first to call attention to the hyperproteinemia (hyperglobulinemia) which may occur in this disease. An increase in serum proteins was found in 10 of the 12 cases studied, and in 9 the globulin was sufficiently increased to cause a reversal of the albumin-globulin ratio. The urine of none of these patients contained Bence-Jones protein. Subsequently Williams and Gutman[5] reported total serum protein values of over 8 gm. % in 26 of 35 patients with lymphogranuloma venereum. In all cases the hyperproteinemia was due to high serum globulin values. In a third paper, Gutman and Williams[3] noted that the Wassermann reaction was anti-complementary in 22% of patients who gave positive Frei tests. In addition, Gutman and Wise[4] described their results with the formal-gel reaction in relation to the hyperproteinemia of lymphogranuloma venereum as well as in that due to other conditions. A positive test occurred in the majority of cases, if the preparation was allowed to stand for at least several hours, or as long as 24 hours.

In 1937, Rosen, Rosenfeld and Krasnow[10] published a preliminary study of the serum lipids and proteins in lymphogranuloma venereum. They found the lipids definitely lowered. Globulin was always high although the total serum proteins were not always elevated. These authors noted a significant relationship between the duration of the disease and alterations in the protein content of the serum; the longer the duration of the disease, the greater the alteration in the serum proteins.

In this paper, we are reporting the serum protein values in 67 cases of lymphogranuloma venereum. In addition to the serum protein determinations the sedimentation rate, Costa reaction, aldehyde test and "serum and water test" were carried out in many cases. Either the Wassermann or Kahn test, or both, were done in all but one case. Red blood cell counts, hemoglobin and hematocrit determinations were done in over half the cases.

Material. The clinical material consisted of a group of 43 patients from the Vanderbilt University Hospital (V. U. H.), and a group of 24 patients followed at the Nashville General Hospital (N. G. H.) (Tables 1 and 2). Many of the V. U. H. patients had been under observation for years, either as the result of the lymphogranuloma infection, or for other reasons. The cases were accepted for this study consecutively as they appeared in the clinic. No cases in which a definite diagnosis of lymphogranuloma venereum was made were discarded.

The diagnosis of lymphogranuloma venereum was considered established if a clinical picture compatible with either the more acute phases of the infection, or its complications were present and if a positive reaction was obtained with one or more Frei antigens. Frei tests were generally done with more than one antigen. The antigens employed were commercial mouse-brain antigens, and human antigens made by us from bubo-pus or gland emulsions. Some patients were tested with as many as four different antigens for comparative purposes.

The subjects with rectal lesions have been separated into groups according to the nature of the lesions as follows: 1, acute proctitis, those cases which were in the early stages of acute ano-rectal ulceration, and in which no scar tissue had as yet developed; 2, chronic proctitis, those cases of ano-rectal ulceration which had progressed or terminated in extensive scar tissue formation. The cases of chronic proctitis in turn have been further subdivided into (*a*) active, and (*b*) inactive. The term *active* has been applied to those cases of chronic proctitis in which acute or subacute inflammatory reaction exists. This does not *imply* that the inflammatory reaction is caused by the virus of lymphogranuloma venereum. *Inactive* cases of chronic proctitis are those in which no inflammatory reaction is present. We have classified the strictures appearing in the chronic group under the following descriptive headings: diaphragmatic, tubular and funnel.

The duration of symptoms as given in the tables refers to the time elapsed from the onset of symptoms until the date of the first serum protein determination. Other laboratory studies were done within a few days at most of the first protein study.

Method. *Serum proteins* were determined by the colorimetric method of Minot and Keller[7] which gives values similar to those obtained by the Kjeldahl method. At V. U H. the accuracy of this method is checked at intervals by parallel determinations by the micro-Kjeldahl technique, and in this study some of the grossly abnormal values were checked in the same way.

TABLE 1.—DATA ON FEMALE PATIENTS WITH LYMPHOGRANULOMA VENEREUM STUDIED AT VANDERBILT UNIVERSITY HOSPITAL.

Number	Race.	Age.	Diagnosis.	Activity.	Duration of disease.	Date of blood study determinations.	Total serum protein.	Serum albumin.	Serum globulin.	A/G ratio.	Sedimentation rate.	Costa.	Aldehyde.	Serum and water.	Hemoglobin.	Red blood cells.	Hematocrit.	No. of positive Frei tests.	Wassermann and Kahn.
1	C	47	Rectal stric.	Chr. act.	20 yrs.	12/20/37	10.60	3.76	6.84	0.55	22	x	?	?	12.5	3.8	38	3	K –
						3/26/38	11.76	3.68	8.08	0.45									W –
2	C	37	Rectal stric.	Chr. act.	12 yrs.	12/20/37	10.60	2.91	7.69	0.38	24	x	?	1+			32	1	K –
						5/23/38	10.60	3.40	7.20	0.47									W –
3	C	37	Rectal stric.	Chr. act.	11 yrs.	3/15/38	8.15	4.51	3.64	1.23	38	x	–	?	11.0	4.8	36	3	K d
						5/19/38	7.85	4.51	3.34	1.35									W –
4	C	42	Rectal stric.	Chr. act.	10 yrs.	12/ 9/37	9.63	4.10	5.55	0.74	45	x	–	–	11.3	3.6	36	2	K x
						1/ 6/38	8.83	3.92	4.91	0.80									W x
5	C	27	Rectal stric.	Chr. inact.	10 yrs.	1/22/38	9.71	3.84	5.87	0.65	38	x	–	1+		2.1	31	2	K d
						2/ 3/38	9.22	3.68	5.54	0.67									W d
6	C	35	Rectal stric.; genital elephantiasis	Chr. act.	7 yrs.	2/ 1/38	10.10	3.48	6.62	0.53	30	?	–	1+	9.2	3.3	30	1	K –
						2/17/38	9.22	3.33	5.89	0.57									W –
7	C	26	Rectal ulcer; vaginal stric.	Chr. act.	7 yrs.	12/15/37	9.63	3.68	5.95	0.62	34	x	–	–	8.9	2.7	29	5	K –
						2/10/38	11.16	3.92	7.24	0.55									
8	C	29	Rectal stric.	Chr. inact.	6 yrs.	12/30/37	9.22	4.10	5.12	0.81	32	x	?	?	9.2	3.8	28	3	K –
						2/10/38	9.22	3.92	5.30	0.74									
9	C	36	Rectal stric.; rectal vaginal fistula	Chr. inact.	5 yrs.	2/ 1/38	10.10	4.19	5.91	0.71	18	–	–	–	9.1	3.8	31	2	K –
						2/10/38	9.63	3.92	5.71	0.69									
10	W	36	Rectal stric.	Chr. act.	4 yrs.	1/13/36	8.49	4.01	4.48	0.89					10.5	4.4		1	K –
																			W –
11	C	31	Rectal stric.	Chr. inact.	2 yrs.	1/20/38	8.83	5.46	3.37	1.62	6	–	–	–	12.2	4.1	43	1	K –
						1/27/38	9.22	5.64	3.58	1.57									W –
12	C	44	Genital elephantiasis	.....	2 yrs.	12/ 9/37	8.49	5.30	3.19	1.66	30	x	–	–	13.1	4.8	44	4	K x
						12/30/37	8.15	5.01	3.14	1.59									W x
						6/10/37	9.22	5.64	3.58	1.58									

13	C	25	Rectal stric.	Chr. act.	7 yrs.	12/22/36	9.63	3.61	6.02	0.60	11				9.3	4.0	35	2	K d
						2/ 5/37	10.60	3.60	7.00	0.52									W –
						2/ 8/37	11.16	4.29	6.87	0.62									
						5/ 5/37	10.10	3.84	6.26	0.61									
14	C	27	Rectal stric.	Chr. act.	3 yrs.	12/13/37	8.83	4.01	4.82	0.83	36	x			11.5	3.4	30	2	K –
						12/23/37	7.57	3.61	3.96	0.92									
15	C	27	Vulval ulcer	.....	1 mo.	1/27/38	10.10	4.01	6.09	0.66	21	?	–	–	9.9	3.5	32	2	K x
						3/ 8/38	10.10	4.29	5.81	0.74									W –
						4/18/38	10.10	4.62	5.98	0.77									
16	C	30	Rectal stric.	Chr. act.	?	3/ 5/38	9.63	3.48	6.15	0.57	34	x	–	–	9.5	2.8	30	4	K x
						4/ 7/38	9.63	3.61	6.02	0.60									W x
17	C	22	Rectal stric.	Chr. act.	?	3/ 3/38	7.57	2.82	4.75	0.59	32	x	–	–	9.4	2.9	28	1	K –
						3/ 5/38	7.85	3.11	4.74	0.66									W –
18	C	25	Proctitis	Acute act.	6 mos.	1/27/38	8.15	4.10	4.05	1.01	41	x	–	–	12.4	4.5	37	2	K x
						2/ 2/38	8.15	4.29	3.86	1.11									W x
						3/10/38	8.15	3.29	4.23	0.78									
19	C	37	Proctitis	Chr. act.	3 mos.	2/ 3/38	9.63	3.76	5.87	0.64	36	x	?	1+	9.7	3.9	31	1	K x
					(?)	2/ 4/38	9.22	3.61	5.61	0.64									W x
20	W	34	Proctitis	Acute act.	3 mos.	2/17/38	7.07	4.51	2.56	1.76	19	x	–	–	11.2	4.2	20	3	K –
						3/ 3/38	6.84	4.40	2.44	1.81									
						5/28/38	8.15	5.46	2.69	2.03									
21	C	23	Rectal stric.	Chr. inact.	1 wk.	4/ 7/38	8.49	4.62	3.87	1.19	34	?	–	–	10.5	3.6	36	2	K x
					(?)	4/26/38	8.15	4.01	4.14	0.97									W x
22	C	27	Vulval ulcer	.....	(?)	4/26/38	8.49	4.19	4.30	0.98	43	x	–	?	11.1	4.0	38	2	K –
						5/19/38	8.49	4.75	3.74	1.27									W –
23	C	31	Proctitis	Chr. act.	1 yr.	4/14/38	8.15	4.75	3.40	1.39	24	x	–	–	10.5	3.2	34	2	K –
					(?)	5/12/38	8.15	5.01	3.14	1.59									
24	C	31	Rectal stric.	Chr. act.	7 yrs.	6/ 9/38	8.49	3.92	4.57	0.86	30	x	–	–			26	2	K –
						6/11/38	8.83	4.10	4.73	0.87									
25	W	55	Rectal stric.	Chr. act.	15 yrs.	10/27/37	7.57	4.51	3.06	1.47	38	–	–	–	10.3	4.3	35	3	K –
						5/26/38	8.15	5.01	3.14	1.59									
26	C	39	Rectal stric.	Chr. act.	1 yr.	4/ 6/38	7.07	3.61	3.41	1.05	40				11.0	3.4	37	3	K –
						6/23/38	8.49	4.51	3.98	1.13									

TABLE 1 (*Continued*).—FEMALE PATIENTS STUDIED AT NASHVILLE GENERAL HOSPITAL.

Number.	Race.	Age.	Diagnosis.	Activity.	Duration of disease.	Date of blood study determinations.	Total serum protein.	Serum albumin.	Serum globulin.	A/G ratio.	Sedimentation rate.	Costa.	Aldehyde.	Serum and water.	Hemoglobin.	Red blood cells.	Hematocrit.	No. of positive Frei tests.	Wassermann and Kahn.
27	W	38	Rectal stric.	Chr. act.	10 yrs.		8.15	4.67	3.48	1.34								4	W –
28	W	28	Rectal stric.	Chr. act.	7 yrs.		9.63	4.63	5.01	0.92								4	W –
29	C	51	Rectal stric.	Chr. act.	11 yrs.		11.77	3.92	7.85	0.49								4	W –
30	C	39	Rectal stric.	Chr. act.	7 yrs.		11.77	7.48	4.29	1.74								4	W –
31	W	34	Rectal stric.	Chr. act.	10 yrs.		10.60	4.62	5.92	0.78								4	W –
32	C	45	Rectal stric.	Chr. act.	9 yrs.		11.77	4.29	7.48	0.57								4	W x
33	C	38	Rectal stric.	Chr. act.	4 yrs.		8.60	4.20	4.40	0.97								4	W –
34	C	28	Rectal stric.	Chr. act.	8 yrs.		8.83	5.30	3.53	1.50								4	W –
35	W	43	Rectal stric.	Chr. act.	6 yrs.		11.77	5.01	6.76	0.75								4	W –
36	C	41	Anal fist.	Chr. act.	5 yrs.		8.83	4.10	4.73	0.87								4	W –
37	C	30	Rectal stric.	Chr. act.	5 yrs.		10.60	3.76	6.84	0.55								4	W –
38	C	27	Rectal stric.	Chr. act.	9 yrs.		13.25	4.29	8.96	0.48								4	W –
39	W	31	Rectal stric.	Chr. act.	7 yrs.		10.60	5.64	4.96	1.14								4	W –
40	C	35	Rectal stric.	Chr. act.	5 yrs.		10.60	7.51	3.09	2.43								4	W –
41	C	32	Rectal stric.	Chr. act.	8 yrs.		10.60	4.75	5.85	0.81								3	W x
42	W	40	Rectal stric.	Chr. inact.	4 yrs.		9.62	5.64	3.99	1.41								4	W x
43	W	41	Rectal stric.	Chr. act.	12 yrs.		11.77	6.01	5.76	1.04								4	W –
44	W	39	Rectal stric.	Chr. inact.	17 yrs.		8.13	5.30	2.83	1.87								4	W x
45	C	27	Rectal stric.	Chr. act.	7 yrs.		8.83	3.76	5.76	0.65								4	?
46	C	46	Rectal stric.	Chr. inact.	7 yrs.		9.63	3.62	6.01	0.60								4	W –
47	W	35	Rectal stric.	Chr. act.	7 yrs.		11.77	5.64	6.13	0.92								4	W –

TABLE 2.—DATA ON MEN WITH LYMPHOGRANULOMA VENEREUM STUDIED AT VANDERBILT UNIVERSITY HOSPITAL.

TABLE 2.—DATA ON MEN WITH LYMPHOGRANULOMA VENEREUM STUDIED AT VANDERBILT UNIVERSITY HOSPITAL.

Number.	Race.	Age.	Diagnosis.	Activity.	Duration of disease.	Date of blood study determinations.	Total serum protein.	Serum albumin.	Serum globulin.	A/G ratio.	Sedimentation rate.	Costa.	Aldehyde.	Serum and water.	Hemoglobin.	Red blood cells.	Hematocrit.	No. of positive Frei tests.	Wassermann and Kahn.
1	C	62	Rectal stric.	Chr. act.	18 yrs.	2/ 7/38	8.49	3.22	5.27	0.61	18	?	–	–	8.0	2.9	24	2	K –
						2/ 9/38	8.15	2.91	5.24	0.56									
2	W	45	Rectal stric.	Chr. act.	5 yrs.	6/17/36	10.10	2.51	7.57	0.33	..				10.5	3.8	..	1	K –
3	C	25	Proctitis	Acute act.	18 mos.	1/19/38	9.22	4.29	4.93	0.87	25	?	–	–	13.4	4.4	44	2	K –
						2/11/38	8.83	4.01	4.82	0.84									
4	C	52	Genital elephantiasis	...	9 yrs.	3/ 3/38	9.63	3.28	6.35	0.52	25	x	?	?	9.0	2.9	28	2	K x
						4/19/38	9.63	3.53	6.10	0.58									W x
5	C	25	Bubo	Healed	2 yrs.	3/ 1/38	8.15	5.15	3.00	1.73								1	K x
																			W x
6	C	38	Bubo	Draining	1 yr.	12/20/37	8.83	5.64	3.19	1.77					12.0	4.7		1	K –
																			W –
7	W	23	Bubo	Acute	6 wks.	1/31/38	8.83	4.75	4.08	1.16	47	x				3.8	37	2	K –
						2/ 3/38	8.15	4.67	3.48	1.35									W –
8	C	18	Bubo	Acute	1 mo.	12/ 8/37	7.85	4.10	3.75	1.09	16	–	–	–	14.0	4.7	44	3	K x
						1/ 3/38	8.49	4.75	3.74	1.26									W x
						3/10/38	8.49	5.01	3.48	1.44									
9	C	24	Bubo	Draining	3 mos.	12/ 7/37	9.63	5.15	4.48	1.15	25	x	–	–	13.1	4.5	42	2	K –
						3/ 8/38	8.15	5.01	3.14	1.59									W –
10	W	34	Bubo	Draining	5 mos.	12/17/37	7.31	5.46	1.85	2.94	3	–	–	?	14.0	4.5	44	1	K x
						2/25/38	7.57	6.44	1.13	5.75									W –
11	W	32	Bubo	Aspirated	6 wks.	3/10/38	7.85	5.15	2.70	1.90	31	x	–	–	13.5	3.7	42	2	K –
						3/18/38	7.31	4.75	2.56	1.86									W –
12	C	41	Bubo	Healed	2 yrs.	1/17/38	7.85	4.40	3.45	1.28	4	–			13.5	4.5	43	2	K –
						1/24/38	8.15	4.75	3.40	1.39									W –
13	C	28	Bubo	Draining	2 wks.	1/14/38	8.15	4.01	4.14	0.97	21	–	–	–	12.2	4.9	39	2	K –
						1/27/38	8.49	3.48	5.01	0.69									
14	C	18	Bubo	Resolved	1 wk.	2/21/38	7.57	5.01	2.56	1.96	14	–	–	–			46	2	K –
						4/26/38	7.85	4.88	2.97	1.65									
						6/11/38	7.31	4.62	2.69	1.73									
15	C	42	Bubo	Excised	1 wk.	3/22/38	7.51	3.92	3.59	1.09	20	x	–	–	11.6	3.1	39	1	K –
						4/16/38	7.85	5.30	2.55	2.04									
16	C	25	Bubo	Aspirated	1 wk.	3/12/38	8.49	5.15	3.34	1.53	19	x	–	–	10.6	5.0	44	3	K –
						5/ 2/38	8.15	4.75	3.40	1.40									
17	C	23	Bubo	Aspirated	1 wk.	3/10/38	9.22	5.15	4.07	1.27	22	?	–	?	11.0	4.3	39	2	K –
						5/ 2/38	8.83	4.51	4.32	1.04									
NASHVILLE GENERAL HOSPITAL CASES.																			
18	W	27	Bubo	Acute	1 wk.		8.83	3.82	5.01	0.76								3	W –
19	C	48	Rectal stric.	Chr. act.	4 yrs.		11.77	3.68	9.09	0.45								4	W –
20	W	46	Rectal stric.	Chr. inact.	14 yrs.		11.07	6.44	4.56	1.41								4	W –

The blood was drawn without stasis. Two or more determinations were made in most of the V. U. H. cases, but not on the same day, because we wished to see what changes, if any, occurred during the course of the illness, especially in the acute stages. As normal values for the serum proteins we have taken those of Peters and Eisenman[9] which are, for total proteins 6 to 8 gm. %, for albumin 4 to 5.5 %, and for globulin 1.4 to 3 %. Youmans, Bell, Donley and Frank[13] found similar values for normal subjects in and around Nashville.

Sedimentation rate was determined by the Wintrobe method. Corrected rates of 20 mm. per hour for women and 9 mm. for men may be considered the upper limits of normal. The Costa reaction which has been used by one of us[6a] in a previous study, was carried out in the usual manner.[1] Napier's[8] technique was used for the aldehyde test, observation being carried out over the period of 1 hour. The "serum and water test" was done as recommended by Sia[11] for use in kala-azar, the readings being made during 1 hour.

The serologic diagnosis of syphilis was made by the Kahn test and by the Kolmer modification of the Wassermann test. In some cases, all of which were negative, the Kahn test only was done.

Hemoglobin determination and red blood cell counts were made in the usual manner. The Wintrobe tube was used in the hematocrit studies.

Results. The findings are summarized in Tables 1 and 2, which also indicate the nature of the lesions, so that the changes in the blood may be compared with the manifestations and duration of the disease. Of the total number of patients, 62 or 92.5% showed, upon at least one occasion, a total protein value of 8 gm. or over, which may be regarded as an elevation. If the value of 3 gm. or over is taken as definite elevation of globulin it was found that 62 (92.5%) of the cases showed this deviation from normal. As a result the albumin-globulin ratio was usually reversed. These changes in many cases are due not only to the elevation of globulin, but also to the depression of albumin values below the level accepted as normal, though, as will be stated below, we do not believe that lowered albumin levels are related to the disease.

Total serum protein and globulin values are summarized in Table 3. The findings are divided according to sex because of the relationship of the protein levels to the type of lesions which may be more or less sex related (this factor will be discussed below). In every case, at one time or another, the total protein was 7.5 gm. % or more. Among the V. U. H. cases the total protein was 8 gm. or more in 76.4% of the males and in 96% of the females. Total protein was above 8 gm. in all of the N. G. H. cases. Serum globulin was 3 gm. % or more in 82.3% of the males and in 96% of the females in the V. U. H. cases and in 100% of the males and in 95.2% of the females in the N. G. H. cases.

The data for the protein values are further broken down in Table 4, in order to show the relationship of serum albumin and globulin to each other. Of the 5 cases with total protein of less than 8 gm., none had a value of less than 7.5 gm. Serum albumin was less than 4 gm. in 17 cases (25.3%), the globulin being over 3 gm. Of those with

albumin values of 4 gm. or more, 73% of all cases, 6 had globulin values of 3 gm. or less.

TABLE 3.—TOTAL SERUM PROTEIN VALUES AND GLOBULIN LEVEL.

	Vanderbilt University Hospital.				Nashville General Hospital.			
	17 males.		26 females.		3 males.		21 females.	
	No.	%.	No.	%.	No.	%.	No.	%.
Total protein:								
7.5 gm. or more	17	100.0	26	100	3	100	21	100.0
8.0 gm. or more	13	76.4	25	96	3	100	21	100.0
Globulin:								
3.0 gm. or more	14	82.3	25	96	3	100	20	95.2

TABLE 4.—RELATIONSHIPS OF TOTAL PROTEINS, ALBUMIN AND GLOBULIN.

	Vanderbilt University Hospital.		Nashville General Hospital.	
	17 males.	26 females.	3 males.	21 females.
Total protein, 8.0 gm. or more:				
Albumin less than 4 gm. / Globulin over 3 gm.	3	7	2	4
Albumin 4 gm. or more / Globulin over 3 gm.	10	17	1	16
Albumin 4 gm. or more / Globulin 3 gm. or less	..	1	..	1
Total protein below 8 gm.:				
Albumin below 4 gm. / Globulin over 3 gm.	..	1	..	..
Albumin 4 gm. or more / Globulin 3 gm. or less	4	..	..	..

It is apparent that no case was found with hypoproteinemia. Further, that hyperglobulinemia is practically the only factor in the elevation of total serum proteins. The instances of depressed serum albumin are probably to be explained on other coincident factors.

The relationship of the total serum proteins, albumin and globulin to the type and activity of the lesions present is shown in Table 5.

TABLE 5.—PROTEINS RELATED TO TYPE AND ACTIVITY OF LESION.

	Total protein 8 gm. or more.			Total protein below 8 gm.		
	Albumin below 4 gm. Globulin over 3 gm.	Albumin 4 gm. or more. Globulin over 3 gm.	Albumin 4 gm. or more. Globulin 3 gm. or less.	Albumin below 4 gm. Globulin over 3 gm.	Albumin 4 gm. or more. Globulin over 3 gm.	Albumin 4 gm. or more. Globulin 3 gm. or less
Active rectal lesion:						
Acute	2	1	1	..	..	..
Chronic	12	21	1	1	1	..
Inactive rectal lesion	2	7	..	..	..	..
Chronic genital lesion	1	3	..	..	..	..
Inguinal bubo:						
Active	1	7	..	..	..	4
Healed	..	2	..	..	..	..

Rectal disease was present in 49 (73.1%) cases. Forty-eight (97.9%) of the 49 cases had total serum proteins, at least at one

time, of over 8 gm., and one had a total protein of over 7.5 gm. All but 2 also showed elevation of globulin to above 3 gm. Seventeen (34.6%) of the 49 had less than 4 gm. of serum albumin so that the hyperglobulinemia is actually more marked than seems apparent from the total protein values. The remainder had normal values for this fraction. In 40 of the 49 cases the disease was considered to be active and in 9 inactive. The activity of the rectal lesions bore no definite relationship to the degree of change in the serum proteins.

In 4 cases, chronic genital lesions only were present, 1 of these being a male with elephantiasis of the genitalia. All 4 cases had an elevation of the total serum proteins due to an increase of the globulin fraction. One had serum albumin of less than 4 gm.

Twelve patients had active buboes, either draining or in the stage of acute lymphadenitis. Two had healed buboes. Elevation of globulin was not as great in patients with buboes alone as in those with chronic genital and rectal lesions. Of the 12 patients with active bubo only 8 (66%), had a serum globulin above 3 gm. One had an albumin below 4 gm. In the 2 patients with healed bubo, infection had occurred 2 years before. They presented ragged inguinal scars, a history compatible with lymphogranuloma venereum and markedly positive Frei tests. Both of these showed a serum globulin of 3 gm. or more, and a total protein of over 8 gm. % the albumin fraction being normal.

Sedimentation Rate. Because it is generally believed that changes in the sedimentation rate are related to alteration in serum proteins, this test was done in 39 of the 43 V. U. H. cases (Tables 1 and 2). Increased rate, though slight in some, occurred in 21 of the 25 females in which the test was done, and in 12 of the 14 males. One of the 2 males with normal rate had had a bubo 2 years before.

It is noteworthy that there was no correlation between the degree of increased rate and the amount of hyperglobulinemia. In the female group were cases with marked increase in serum globulin but with normal sedimentation rates. It is possible that there may be some relationship between the sedimentation rate and activity of the lesion. This is indicated by the fact that practically all the male cases which had active buboes showed an increased rate.

Costa Reaction. This test, also possibly related to serum proteins or their derangements, was carried out in 37 of the 43 cases studied at V. U. H. (Tables 1 and 2). As may be seen from the tables, the results rather closely paralleled those of the sedimentation rate, though the test is probably not quite as sensitive, as suggested by the experience of one of us (R. H. K.) with the test in tuberculosis. In the present study, the Costa test was negative in 5 cases where the sedimentation rate was increased, though in 2 of these there was very slight increase in sedimentation rate. The Costa reaction was questionable in 5 cases in which the sedimentation rate was increased. Among 5 cases with a negative Costa reaction there were 3 in which

there was definite elevation of the serum globulin. Therefore, as in the case of the sedimentation rate, there was no correlation between the degree of protein derangement and a positive or negative Costa reaction.

Aldehyde Test. A positive aldehyde test, as described by Napier in untreated kala-azar, was not obtained in any of the 34 cases in which it was done. Opaque solidification of serum never occurred even after some hours. In 5 cases, all showing hyperglobulinemia, the test was recorded as questionable. In such cases, the serum jellied and was slightly cloudy after 30 minutes or more. Napier described this as occurring in some cases of tuberculosis, leprosy and malaria.

Serum and Water Precipitation Test. This test was also carried out in 34 cases, with observations at 5, 15, 30, and 60-minute intervals. In no case did a sediment form which Sia described as a definitely positive test. At the end of an hour, in 4 cases, a haziness was found, and the test was recorded as a 1+. Hyperglobulinemia was present in all those patients who showed a 1+ test, and in 5 of those with questionable ones.

Wassermann and Kahn Tests. Because of a possible relation of these tests to the globulin fraction of the serum proteins and because Gutman and Williams found the Wassermann reaction to be anti-complementary in 22% of 74 Frei positive cases, the results in our cases are of interest.

Of the 43 V. U. H. cases, none were found to have anti-complementary Wassermann reactions. Both Wassermann and Kahn tests were negative in 13 cases, and both positive in 9 cases. The Kahn test alone was negative in 16 additional cases. Both tests were doubtful in 1 case, the Wassermann was negative and the Kahn doubtful in 2 cases, and the Wassermann negative and Kahn positive in 2 cases.

In the N. G. H. group of 24 cases, the Wassermann test was negative in 19 instances, positive in 4, and not done in 1.

Recently, one of us[6b] reviewed the cases of rectal stricture treated in V. U. H. since 1926. Most of these cases were not proven by the Frei test, but analysis of the history and physical findings made it seem reasonable that a certain percentage of these were due to lymphogranuloma venereum. In those selected as probably being cases of this disease, the Wassermann reaction was negative in 29 and positive in 16, 2 were Wassermann and Kahn positive, 6 were Wassermann negative and Kahn positive, 1 was Wassermann doubtful and Kahn positive.

Our findings do not agree with those of Gutman and Williams as regards the frequency of anti-complementary Wassermann reactions in lymphogranuloma venereum. (Since this study was completed an anti-complementary Wassermann and positive Kahn test were found in a patient with bubo and hyperglobulinemia.)

Hemoglobin, Red Cell Counts and Hematocrit Studies. A study of the tables indicates that secondary anemia is frequent among the patients suffering from active forms of lymphogranuloma venereum. This is especially true in females in whom anemia was greater than in males, and more frequent. In fact practically no female was found with a normal hemoglobin and red cell count. It should be pointed out, however, that chronic manifestations of lymphogranuloma venereum, such as proctitis or rectal stricture, are not the only possible causes of this anemia. Secondary anemia is generally not uncommon among our clinic patients, especially among females, in whom childbearing and poor diet lead to an iron deficiency.

These examinations were carried out not because we expected to find any definite relationship of the state of hemoglobin, red cells or hematocrit reading to the disease under consideration, but to satisfy ourselves that the hyperproteinemia was not related to dehydration and blood concentration. To be sure, this did not have to be considered seriously because of the almost constant hyperglobulinemia. (White blood cell counts are not given since they showed only the usual changes which occur in lymphogranuloma venereum.)

Non-protein Nitrogen. In a small number of cases with hyperproteinemia the non-protein nitrogen was determined. In no case was it found to be elevated.

Discussion. Hyperproteinemia due to hyperglobulinemia is not specifically restricted to lymphogranuloma venereum. It has long been known that increase in the serum proteins may occur in a number of diseases, aside from those due to dehydration alone. Multiple myeloma has been recognized as a cause of hyperglobulinemia. (Incidentally no Bence-Jones protein was found in those of our cases of lymphogranuloma venereum so tested.) Kala-azar is associated with hyperglobulinemia. Liver disease also may cause an abnormal elevation of serum globulin. Peters and Eisenman[9] found increased globulin in ulcerative pulmonary tuberculosis, and in syphilis, especially of the gummatous types.

It is apparent that the elevation of serum globulin to above normal levels, with an abnormally high total protein in those whose albumin is normal, is a frequent occurrence in the various stages of lymphogranuloma venereum.

The likelihood of a dietary deficiency causing a drop in albumin in many of these patients is supported by the frequency of anemia in the women. However, a study of the tables indicates that the globulin elevation is not compensatory for the drop in serum albumin because the latter was not lowered in the majority of the chronic cases and in almost none of those with buboes. Also it will be noted (Tables 1 and 2) that with the elevation of the total serum proteins there is a corresponding increase in serum globulin in most cases without a lowering of the albumin fraction, again indicating that the increase in globulin does not occur as a compensatory reaction.

It is worthy of emphasis that protein derangement occurs not only in the presence of rectal disease, but also in association with other lesions due to the disease. Therefore, the rectal or bowel lesions have no exclusive relationship to abnormalities in the serum proteins.

Elevation of serum globulin may appear early in the disease, as shown in Case 7 (Table 2), a young white male seen in the stage of bubo, in whom the protein change occurred before the Frei test became positive. It also may persist for many years, if not permanently, as may be seen from Tables 1 and 2 where the duration of the disease is recorded. Furthermore, the increase in globulin tends to become greater as time passes, and the highest values are found in cases of years standing. Apparently the derangement persists with what appear to be completely healed lesions.

The change in the proteins is not related to the activity of the lesion, though the globulin level is less often as high in active bubo cases as in cases with lesions of many years' duration. Possibly this means the disease has not been established sufficiently long enough for the maximum change to have taken place.

We offer no explanation as to the possible cause of the derangement of the serum proteins which we observed. As a control for the involvement of lymphatic tissue, we have made serum protein determinations in a number of cases of chancroid with bubo, and of secondary syphilis with especially extensive lymphoid involvement and have found no instances of changes in the protein fractions. However, we are aware of the case of a female negro child in whom there was proven tuberculous lymphadenitis and hyperglobulinemia. In light of the fact that lymphogranuloma venereum as another genito-infectious disease is not infrequent in syphilitics, some of the examples of hyperglobulinemia which have been reported in the past as occurring in syphilis may well have been due to coincident lymphogranuloma venereum.

Though the hyperproteinemia due to hyperglobulinemia in lymphogranuloma venereum is not a specific finding, it is a very constant finding and so is of some diagnostic value. Further, it is a remarkable fact that derangement of proteins persists for many years, and is probably a permanent change. Whether this indicates persistent infection cannot be determined at this time.

Summary. 1. Blood studies in 67 cases of lymphogranuloma venereum have been presented.

2. At one time or another 62 cases showed a total serum protein of 8 gm. or more, and in 62 the serum globulin was 3 gm. or more.

3. Derangement of the serum protein occurs at any stage of the disease and apparently persists permanently. Such changes occur in cases of buboes, chronic genital lesions, and in acute and chronic proctitis as well as in rectal strictures.

4. Other tests possibly related to serum proteins show either no changes or inconsistent changes.

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STUDIES ON THE PHYTOTOXIC INDEX.

III. An Evaluation of the Method With Reference to Depressed Psychotic Patients.

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In previous investigations by use of the phytotoxic method of Macht[4] we obtained results which disagreed with those of other workers. We found that the blood and urine from male schizophrenic patients who were otherwise healthy were not more toxic to Lupinus albus seedlings than were the blood and urine from normal, healthy men[1a] and that the phytotoxicity of the blood of normal, healthy women did not vary materially whether taken during the inter-menstrual or intra-menstrual periods.[1b] These findings were at variance with those of Tscherkes and Mangubi[8] and Macht and Lubin.[5] These discrepancies led us to make a careful study of all the variables concerned in the obtaining of the phytotoxic index. To obtain this information we have determined the rate of growth of the Lupinus albus seedlings and also the effect of the initial root length and various temperatures on the index. The variation in toxicity of blood serum at different concentrations and the minimum number of seedlings necessary to give a statistically valid test were also determined.

As one of us (J. M. L.) in an earlier study in collaboration with Macht[5] had found that the serum of depressed patients was toxic to the Lupinus albus seedlings, it was decided to use depressed patients in the present study.

Method. Ten male patients were selected and paired with an equal number of normal male subjects. The selections were made by the attending psychiatrist on the basis of the depth of the depression and only those showing severe depression were utilized. Inasmuch as other workers have reported that pernicious anemia[3], pemphigus,[6] and otosclerosis[7] caused an increase in blood phytotoxicity, no patient was chosen who had any indications of these diseases. The group therefore represented as nearly as possible a sample of depressed psychotic patients without complicating organic diseases.

Because the "phytotoxic index" depends on the rate of growth of the root tip of the Lupinus albus seedling, it is essential that the data be collected in such a way as to permit control of the inherent biologic variables. Macht and his followers used a 1% solution of the test substance in a 50% strength of Shive solution.[4,5] No information is available to indicate that this is the optimal concentration. The ideal dilution is one which contains the minimum amount of the test substance which will yield a quantitatively significant index.

We have modified the technique to afford better control than in the original method. Each blood sample was defibrinated and diluted with water to make three different concentrations, and then mixed with an equal volume of Shive solution. The final blood dilutions were: ½%, 1%, and 2%. The phytotoxic index for each patient per blood concentration was obtained using 25 test seedlings for each series. From these figures the phytotoxic-index means of the entire group per strength of blood solution were obtained. The means were 0.871 ± 0.018, 0.853 ± 0.014, and $0.590 \pm .010$ respectively, and the corresponding standard deviations were 0.136 ± 0.013, 0.157 ± 0.010, and 0.093 ± 0.007.

By the criterion of the standard error, the difference between the means of the ½% and the 1% strengths was not significant. On the other hand, the difference between the mean of the 2% solutions and the means of either the 1 or ½% was significant. It is apparent that the toxic action of the blood is slight in the lower concentrations and that 2% is the minimal strength necessary to retard appreciably the rate of growth. We therefore used 2% solutions for all our tests.

In order to study the variability of the seedlings in the same solution the mean root growth was determined when different numbers of seedlings were used. It was found that in order to have an adequate representation of different growth types and thus minimize the inherent variability between tests, it was necessary to have at least 20 seedlings in each test. Our studies were therefore run on the basis of 25 seedlings to allow for occasional spoiling of certain tests by broken seedlings or complete failure to grow.

In order to determine the effect of initial root length in the test, the rate of growth was determined by the following procedure.

Twenty-five seedlings were placed in moss for germination. They were examined every 12 hours until the roots had definitely started growth, which in the majority of instances, required 48 hours. The seedlings were then placed in half-strength Shive solution exactly as in the actual tests. The root lengths were measured and recorded every 12 hours until branching occurred, which was roughly around 8 days. The room temperature was generally recorded once a day.

A growth curve of the Gompertz type, $Y = 14\ (1.07)^{0.52^x}$, was calculated from the data thus obtained and gave a good fit to the observed values. From this curve (Fig. 1) it is noted that the steepest portion and therefore the most rapid growth occurred shortly after the roots obtained a length of 2 cm. The growth from this point to about 7 cm. appeared to be at a uniform rate and then there occurred a gradual decrease in the rate of growth as indicated by a flattening of the curve. It is evident, therefore, that seeds

should be chosen for testing so that their lengths will fall between these limits during the test. Furthermore, the seeds should be so distributed that the means of the root lengths of each series being tested should be equal to that of the Shive control. The average initial length of the roots taken in the test was 3.07 cm., and in no case were tests made with beans of an average root length of less than 2.0 cm. We can state, therefore, that the tests were conducted on beans at such a stage of growth that the curvature at the extremes of the growth curve was not an important factor in the final result.

Further precautions were taken. The technician, during her menstrual periods, used rubber gloves to prevent palmar perspiration contaminating the seedlings.[15b] The technique was performed by the same person during the entire study.

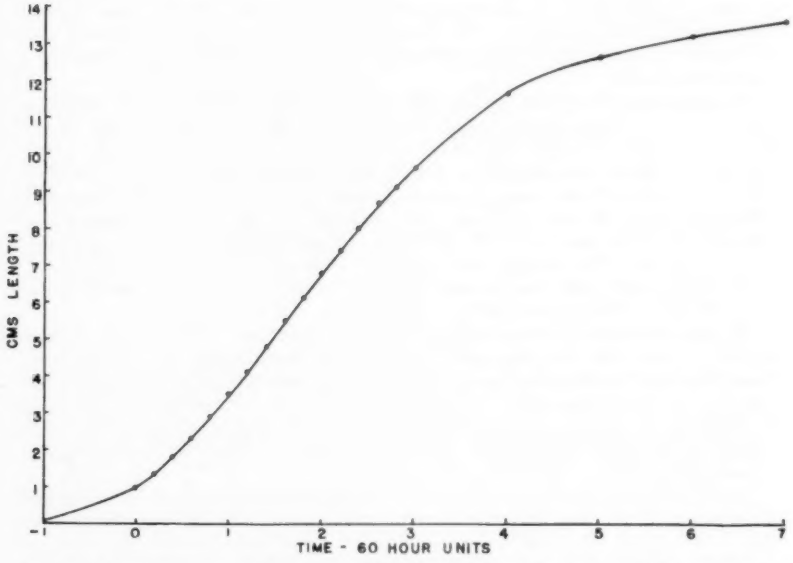

FIG. 1.—Gompertz curve $Y = 14(1{,}07)^{0.52x}$ fitted to growth of Lupinus albus seedlings, 20° C.

In previous studies most investigators have not run normal serums at the same time as their test serums but have taken the value of 70 to 80% as the phytotoxic index of normal blood serum. As the tests are run at room temperature the possibility arises that tests run during warm weather may not give the same results as those run during cold weather because of a differential effect of the toxic materials on the root growth at different temperatures.

In order to investigate this possibility, the 10 pairs of patients and normal subjects were tested against Shive solution under different conditions of temperature and initial root length. The seedlings were divided into two groups, one having long roots and the other having short roots. Since all the short roots were not of exactly the same length, we get grouping into lengths within each

major group. These groups were then distributed into six divisions containing 25 beans in such a way, however, that the average length of roots in each division was approximately the same for the patients, normal subjects, and Shive solutions in both the warm and cold temperature groups. Thus the 6 shortest beans were assigned to warm and cold temperatures for patient, control, and Shive solutions, then the next 6, and so on until all the beans were distributed. Because of occasional failure of some of the beans to grow or because of accidents, and so on, it was not possible to obtain 25 seedlings in each set and the final analyses were made on the results from 18 seedlings.

A test of depressed patient, control, and Shive's solution were always run simultaneously and form what we shall call a set. Each set was run at different times and on a different lot of beans. While these lots were not of exactly the same length, or possibly inherent growth capacity where the temperature conditions of the experimental chamber were the same from set to set, the lots were the same for the 3 members of each set. From set to set the short roots averaged initially from 1.7 cm. to 3.9 cm. length, while the long roots averaged 3.5 to 5.8 cm. This lack of consistency was due to inherent difficulty of obtaining uniform growth in the germinating seeds, and introduced some uncontrolled variation between the sets. The roots assigned to long and short groups did not differ in length to the same extent for all sets. The average difference between the long and short groups varied from 1.1 cm. to 1.9 cm. The temperature of the cold room varied between 15° and 20° C. while that of the warm room varied between 26° and 35° C.

TABLE 1.—AVERAGE GAINS IN ROOT LENGTH PERTAINING TO BEAN SEEDLINGS GROWN IN PATIENT BLOOD, CONTROL BLOOD, AND SHIVE NUTRIENT SOLUTION; 18 ROOTS AT EACH OF TWO TEMPERATURES AT EACH OF TWO LENGTHS FOR EACH OF 10 PATIENTS, 10 CONTROLS, 10 SHIVE SOLUTION.

	Short.				Long.			
	Warm.		Cold.		Warm.		Cold.	
	Mm.	P.I.	Mm.	P.I.	Mm.	P.I.	Mm.	P.I.
Patients . . .	6.20	92.7	4.28	93.8	4.87	89.0	4.25	109.0
Controls . . .	5.62	84.0	4.01	88.9	4.52	82.4	3.84	98.7
Shives	6.69	..	4.51	..	5.47	..	3.89	

The average gains in root length for patients, controls, and Shive's solutions for each temperature and each length separately and the phytotoxic indices arising from these values are given in Table 1.

The increase in root length varies significantly from one set of roots to the next both in respect to initial root length and temperature. We find that for any given set where the ranges of lengths are small, the initial root length is relatively unimportant in determining the subsequent gain, but that where great differences in initial length occur as between long and short sets, the final gain is significantly influenced by this factor. Thus the average difference in gain for all sets between long and short roots is 0.74 mm. The

difference is more marked in the warm room where the short roots gained an average of 1.22 mm. in excess of the long roots, than in the cold room where the difference is only 0.27 mm.

The effect of temperature is even more marked than that of initial length, the average gain in the warm room being 1.44 mm. more than in the cold room. In this case, too, the short roots were affected more than the long ones, as the average difference for the short roots is 1.92 mm. while for the long roots it is 0.95 mm. Both of these differences are highly significant, as is the difference between the effects amounting to 0.97.

The phytotoxic index shows great variation from set to set, the highest index for both patients and normal subjects being obtained for long roots in the cold room, and the lowest for long roots in the warm room. Even for short roots the index is higher for those growing in the cold room though here the difference is slight. It is apparent, therefore, that the phytotoxic index is not constant as the effect of temperature causes a more marked effect on the seeds growing in Shrive solution than it does on those growing in blood. Furthermore, the index for normal individuals is not 0.75 as given by Macht but varies from 0.99 to 0.40[1] depending on the conditions under which it is obtained. There is no consistency in the average difference in growth between Shive and blood from set to set so that the mean difference of 0.45 mm. cannot be regarded as significant. Furthermore the rate of growth of the seeds was greater in the patients' bloods than in the control blood, although the difference between them, 0.39 mm., is not significant. However, if we compare the growth of the long roots for the patients in the warm room with that of the control subjects in the cold room we obtain a difference of 1.03 mm. in length and 10.3 in the phytotoxic index, and these differences are significant.

From these results it would appear that the assumption that change in the variables of temperature and root length would affect the rate of growth of the seedlings in Shive solution to the same extent as those in the test solutions, and therefore the phytotoxic index would not be altered, cannot be maintained. It is evident, therefore, that no comparison as to toxicity can be made between two groups of subjects by means of the growth of Lupinus albus seedlings, unless they are studied with an adequate number of seeds—at least 20—under identical conditions of temperature, root length, and seed lot.

Summary. A study was made of the factors influencing the growth of Lupinus albus seedlings used in the phytotoxic index of Macht, using bloods taken from normal and depressed psychotic male subjects. It was found that the effect of variation of temperature and initial root length was not of the same magnitude on the roots in straight Shive solution as compared with those in Shive solution containing 2% of blood.

The phytotoxic index of normal individuals was found to vary from 0.40 to 0.98, that of depressed patients from 0.89 to 1.09.

Cold environment was found to retard seeds growing in Shive solution more than those growing in blood and to have a greater effect on long roots than on short ones.

Conclusions. 1. No comparison of phytotoxic indices is valid unless the tests are made with at least 20 seedlings in each set of Shive solution, control solution, and test solution, and the initial root lengths and other conditions of growth are matched in each set.

2. The phytotoxic index of normal subjects is not constant and cannot be given as 0.75 as stated by Macht.

3. The toxicity of blood from depressed patients is not greater than that of normal subjects.

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THE ELECTROCARDIOGRAM DURING INSULIN SHOCK TREATMENT OF SCHIZOPHRENIA AND OTHER PSYCHOSES.

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That hypoglycemic shock may have an effect on the heart and circulation has been established by many observers. This conclusion is the result of studies of the effect of moderate grades of hypoglycemia on patients having varying grades of myocardial disease. The increasing use of extreme grades of insulin shock in the treatment of schizophrenia and allied disorders makes it important to review the cardiac effects of this therapy not only in the presence of myocardial disease but in normal hearts as well.

Previous electrocardiographic studies during insulin shock, made chiefly in the presence of myocardial disease, have revealed inversion of the *T* waves, extrasystoles, auricular fibrillation, disturbances

in the auriculo-ventricular condition and lengthening of the *QT* interval.[10,11,17,21–23]

Studies on the electrocardiographic effects following insulin shock treatment in schizophrenia are relatively few and largely confined to foreign literature. Hadorn[9] and Bieglbach and Dussick[3] have observed depression of the *ST* intervals, flattening and inversion of the *T* waves prolongation of the *QT* interval and extrasystoles.

The object of this presentation is to record the electrocardiographic findings in 40 patients in whom 58 studies were performed during insulin shock therapy. These studies were made in young subjects of mental disorder, chiefly between the ages of 20 and 30. Before acceptance for this type of therapy, these patients were submitted to a complete physical examination including an orthodiagram and one or more control electrocardiograms. Only patients with normal electrocardiograms and negative cardiac findings were accepted for this study. On the day of this study, the patients were given a dose of insulin, ranging from 35 to 340 units. Electrocardiograms with simultaneous blood sugars were taken at varying periods of time, usually 3, 4 and 5 hours after insulin administration. In most instances, the patients were in coma at the time the electrocardiograms were taken; a tracing was taken at the termination of the coma. In those cases that showed electrocardiographic changes, successive tracings were taken during the day until the tracing returned to a normal form. The tracings were obtained during various stages of shock therapy which was continued 6 times a week for approximately 8 weeks.

Table 1.—Age, Sex and Type of Mental Disorder.

Age.	Cases.
10 to 19	12
20 to 29	21
30 to 39	7
Total	40

The sexes were equally divided. In this series, there were 35 cases of dementia precox, 4 were manic-depressives and 1 patient had paresis.

Insulin Dosage. The usual routine of therapy was to start each patient with 20 units of insulin on a fasting stomach and increase the dose 10 units daily until the patient went into hypoglycemic coma; this usually occurred within 3 hours after the administration of insulin, if the dosage was adequate. The determination of the state of "coma" was made arbitrarily by the inability of the patients to respond to such stimuli as shaking, pin-prick, and so on, and also the findings of loss of swallowing or corneal reflexes. Usually this was obtained with an average dose of 90 units of insulin. Some cases, however, required as high as 340 units (Case 10) to produce

this state. They were kept on this shock dose during the remainder of the period of treatment.

The Blood Sugar During Insulin Shock Therapy. The initial effect of an adequate amount of insulin was seen ½ to ¾ of an hour following injection and the maximum fall in the blood sugar was observed in 2 to 3 hours. Blood sugar values of less than 20 mg. per 100 cc. were unusual at this point; the usual range in our series was between 20 to 35 mg. per 100 cc. There then occurred a gradual rise in the blood sugar even though the patient was not given carbohydrate. This is presumably due to the compensatory action of adrenalin. There is no necessary relation between the depth of coma and the level of the blood sugar. Patients may remain in coma or develop deeper coma in spite of a gradually rising blood sugar.

TABLE 2.—SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS.

	Cases.
Depression of ST segment:	
*ST*1, 2 and 3	1
*ST*1 and 2	4
*ST*2 and 3	12
*ST*1	1
*ST*2	4
Total	22
Changes in the T waves:	
Low *T*1	3
Low *T*2	2
Prolonged QT interval	6
Arrhythmias:	
Auricular fibrillation	2
Auricular extrasystoles	1
Shifting pacemaker	2
Total	38

Minor Changes.

Arrhythmias:	
Sinus arrhythmias with other changes	8
(alone in 5 cases) Total	13
Sinus bradycardia	4
(alone in 2 cases) Total	6
Sino-auricular block	5
P waves:	
Split *P*2	2
Inverted *P*2 and 3	1
Total	3
Slurred QRS complexes	2

Electrocardiographic Changes. Alterations in the electrocardiogram more or less marked were obtained in 38 of 59 shock treatments (60%). These are detailed in Table 2. The significant changes are as follows: 1, depression of *ST* segment; 2, flattening of the *T* waves; 3, prolongation of *QT* interval; 4, arrhythmias; auricular fibrillation, auricular extrasystoles, shifting pacemaker and sino-auricular heart block; 5, *P* wave changes and slurring of the *QRS* complexes.

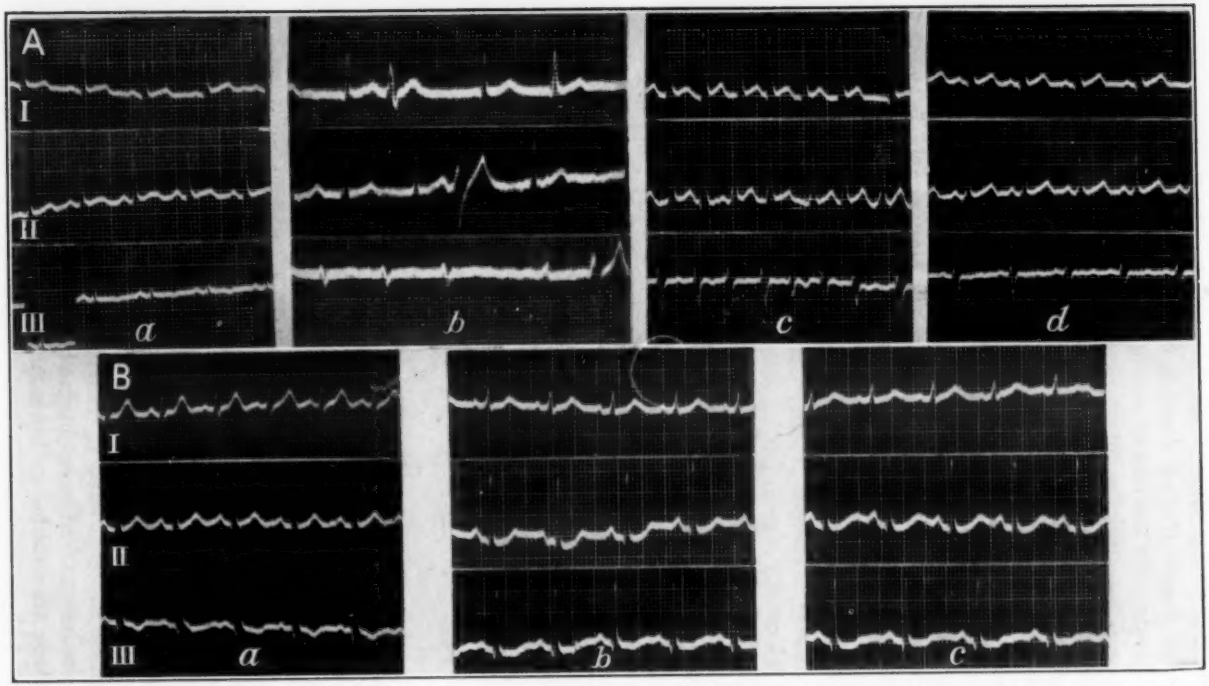

FIG. 1A.—Case 18, aged 31, male, dementia precox, paranoid. (*a*) Control, 1/22/37, 4 P.M. normal tracing. This patient received *75 units* of insulin at 7:30 A.M., 5/23/37. (*b*) 11:20 A.M. patient in coma. Blood sugar 15 mg. %. *Auricular fibrillation* is present with occasional ventricular extrasystoles. Average rate, 75 per minute. This patient's coma was terminated at 12:45 P.M. (*c*) 4 P.M. *Auricular fibrillation* persists, rate averages 160 per minute. Patient manifested no symptoms of cardiac embarrassment. (*d*) 5/24/37. 11 A.M. normal rhythm.

FIG. 1B.—Case 35, female, aged 20, dementia precox, catatonic. (*a*) Control 12/6/37, 4 P.M. normal tracing. This patient received *140 units* insulin at 7:30 A.M., 12/7/37. (*b*) 11:30 A.M. blood sugar 22 mg. %. Patient in coma. *Note depression of ST intervals in Leads II and III.* (*c*) 12 noon blood sugar 26 mg. %. Patient in coma. *Note depression of ST2 and 3 and long QT interval*

No changes were observed in 7 shock treatments besides sinus arrhythmia or sinus bradycardia. The latter is not to be regarded as an important change. No electrocardiographic changes were observed in 13 shock treatments. We can, therefore, state that no significant electrocardiographic changes were obtained in 20 of the 58 treatments (35%).

The most marked electrocardiographic changes were recorded usually during the period of the lowest blood sugar levels; but few exceptions were observed. In most instances, the changes returned to normal with return of the blood sugar to normal levels. In some, however, it took 2 to 3 hours for these changes to disappear. In 2 cases which developed auricular fibrillation, 1 returned to normal rhythm within 4 hours, and the other within 24 hours. In none of our cases were the changes permanent. Hadorn[9] has noted some instances, however, where the changes have not been reversible.

Discussion. In view of the profound changes in the organism as a whole during severe hypoglycemia in which the heart muscle must participate, it appears almost inevitable that electrocardiographic changes should be recorded. The presence of the electrocardiographic changes noted above are usually considered evidence of some derangement in the myocardium, either toxic or the result of disease. Their reversible character in these patients would suggest that whatever is the cause of the disturbance in the heart, it is transient in nature.

The insulin shock treatment above described produces profound alterations in the chemistry of the body, some of which will be described presently. We feel that all of the systemic alterations to be mentioned could be possible factors in causing the electrocardiographic changes described. Whether or not they are the actual cause of these changes we cannot definitely state; however, in a discussion of the possible factors responsible for the electrocardiographic changes, the following should be taken into consideration.

1. *Hypoglycemia.** The blood sugar falls to an extremely low level in these patients (10 to 35 mg. per 100 cc.); frequently there is no available glucose in the blood stream. The patient remains in the hypoglycemic state for about 4 to 5 hours. A depletion of the glycogen store takes place first in the liver, then in the muscles and finally in the heart. In addition, the work of the heart is increased; the minute volume is increased 15% to 45%.[3,6,15] This increased work has been ascribed as resulting from a compensatory discharge of adrenalin. Peripheral dilatation is indicated by the presence of capillary pulsation.[6] Since oxygen consumption is increased in hypoglycemia, the bright red color and high oxygen content of the venous blood is evidence of a more rapid blood flow. The pulse

* The increased cardiac output, the increased pulse pressure and other circulatory phenomena indicate that insulin hypoglycemia does not produce circulatory shock in its usual sense.

11 A.M. normal rhythm.

FIG. 1*B*.—Case 35, female, aged 20, dementia precox, catatonic. (*a*) Control 12/6/37, 4 P.M. normal tracing. This patient received 140 units insulin at 7:30 A.M., 12/7/37. (*b*) 11:30 A.M. blood sugar 22 mg. %. Patient in coma. *Note depression of ST interval in leads II and III.* (*c*) 12 noon blood sugar 20 mg. %. Patient in coma. *Note depression of ST's and T's and long QT interval in leads II and III.*

rate is accelerated; the systolic pressure may be elevated and there is an average increase in pulse pressure of 73%. According to the figures of Cruickshank and Patterson,[4] the normal heart utilizes

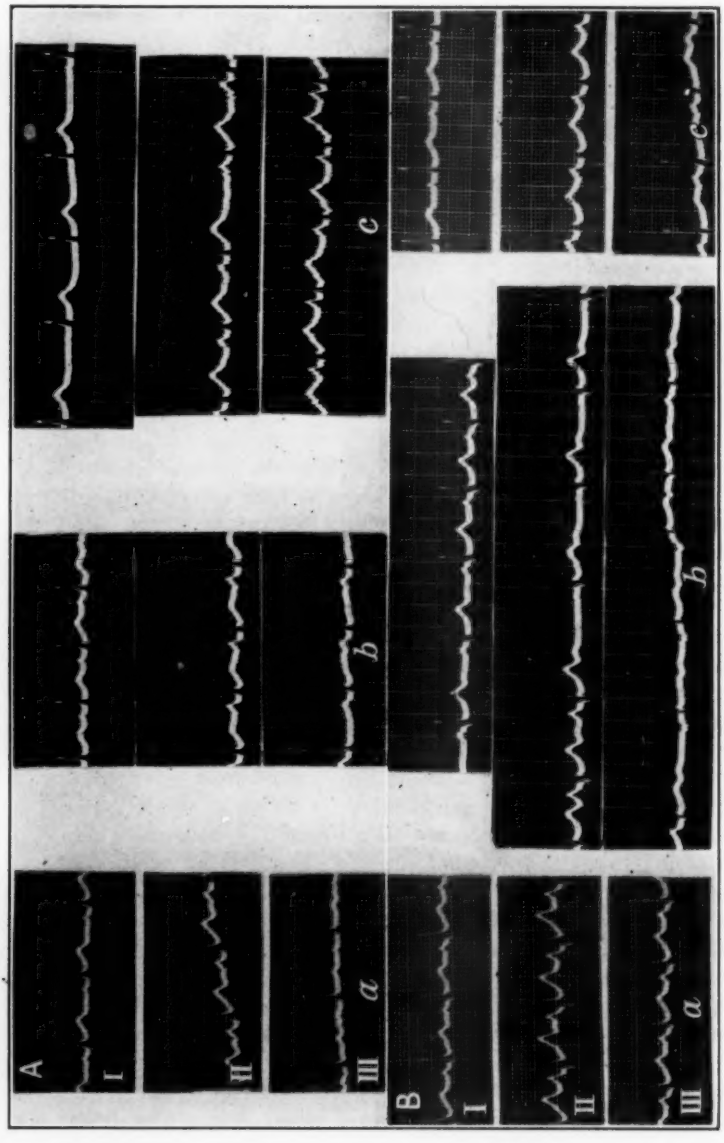

FIG. 2A.—Case 2, aged 26, male, dementia precox, paranoid. (*a*) Control 11/29/37. 4 P.M. normal tracing. The patient received *100 units* insulin at 7:30 A.M., 11/30/37. (*b*) 11:05 A.M., blood sugar 22 mg. %. Patient in coma. *Note depressed ST2 and 3 and long QT interval.* (*c*) 12:05 P.M. in coma. Note presence of *sinus arrhythmia and lower ventricular rate.*

FIG. 2B.—Case 30, aged 30, male, dementia precox, paranoid. (*a*) Control 11/8/37, 4 P.M. normal tracing. This patient received *130 units* insulin at 7:30 A.M., 11/9/37. (*b*) 11 A.M., blood sugar 26 mg. %. Patient in coma. Note *bifid P1 and 3*; change of pacemaker in Leads II and III, accompanied by change in rate. (*c*) 12:05 P.M., patient had been terminated 5 minutes before. Note depression of *ST1, 2 and 3* and prolonged *QT* in Leads II and III.

1.87 mg. of sugar per gm. per hour. Thus with increasing demands for effort come decreasing supplies of available energy in the form of combustible glucose.

2. *Dehydration.* During the course of a single shock treatment, these patients may lose as much as 5 pounds of water; there results consequently a marked hemoconcentration. The blood volume is diminished, particularly the plasma volume.[3] There is a rise in the erythrocyte, hemoglobin and hematocrit values. The changes reported are large enough to affect concentration of electrolytes and non-electrolytes of the blood.[14]

3. *Alteration in Electrolytes.* Marked disturbances in electrolytes have been observed. There is an increase in the pH of the blood with a tendency toward alkalosis; the potassium content of the serum falls and the sodium content rises; the serum calcium rises slightly or is constant; the magnesium is not uniformly affected; the inorganic phosphates decrease and a decrease in chlorides has been reported.[1,3,8]

4. *Effect of Insulin per se.* The administration of insulin *per se* has been said to be responsible for some of the electrocardiographic changes observed. Studies by Schaffer, Bucka and Friedlander,[21] von Haynal, Vidovsky and Györgi,[11] and Soskin, Katz, Strousse and Rubinfeld[22] have been reported in which the administration of insulin immediately covered by sufficient glucose to prevent hypoglycemia in a patient with cardiovascular disease also resulted in electrocardiographic changes. These alterations have been ascribed by these workers to the direct effect of insulin upon the myocardium. It is extremely difficult to dissociate the direct effects of insulin and those due to its hypoglycemic effects in the experiments of the above type, since one cannot be certain that the absence of hypoglycemia in the peripheral blood by the administration of glucose mirrors exactly the conditions surrounding the tissues of the heart. For this reason we doubt whether the electrocardiographic changes can be ascribed to a direct insulin effect upon the myocardium.

5. *Anoxemia.* It has been shown that a similarity exists between the effects of hypoglycemia and those of oxygen deficiency produced by inhalation of gas mixtures. The investigations of Holmes,[13] Wortis,[24] Dameshek and Myerson[5] and Himwich[12] and his collaborators suggest that lowering the blood sugar reduces the oxygen consumption of the brain and that oxidation in this organ is lowered when the supply of either oxygen or dextrose is reduced. This statement does not apply to an equal degree to the heart which can metabolize proteins and fats. However, the lack of available carbohydrate and the increased work of the heart during hypoglycemic shock of long duration would suggest that anoxemia may be a factor in producing the cardiac effects. The *ST* interval changes produced are similar to those observed by Rothchild and Kissin[19] and others after experimental anoxemia in the human subject.

6. *Cerebral Alterations.* Profound changes occur in cerebral metabolism during hypoglycemia and the resultant coma. It has been fairly well established that the heart may be indirectly affected by alterations in the brain. That profound functional alterations

received *130 units* insulin at 7:30 A.M., 11/9/37. (6) 11 A.M., blood sugar 26 mg. %. Patient in shock. (c) 12:05 P.M., patient had been terminated 5 minutes change of pacemaker in Leads II and III, accompanied by change in rate. before. Note depression of *ST*1, 2 and 3 and prolonged *QT* in Leads II and III.

occur in the metabolism of the brain cells during hypoglycemia has been established; it is the basis of the insulin shock therapy. These changes may be responsible in part at least, for some of the electrocardiographic alterations observed.

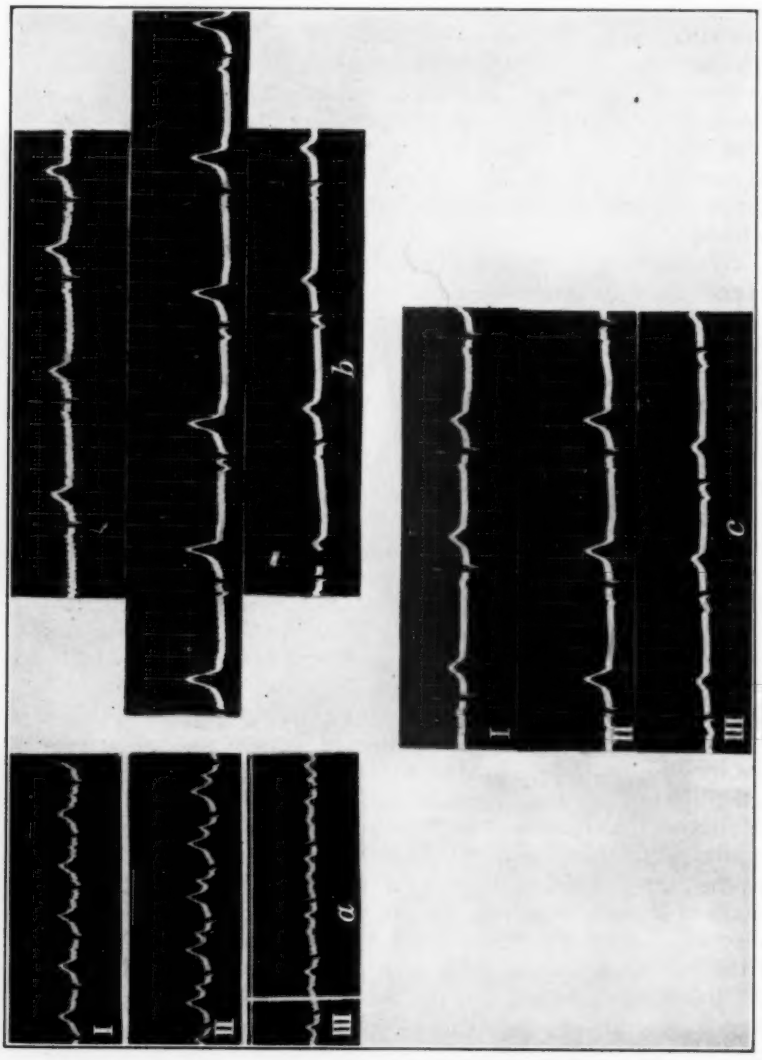

FIG. 3.—Case 36, aged 22, female, dementia præcox, paranoid. (*a*) Control 12/6/37, 4 P.M. This patient received *145 units* insulin at 7:30 A.M., 12/7/37. (*b*) 11:34 A.M. in coma, blood sugar 30 mg. %. Note slow ventricular rate, 50 per minute, and shifting pacemaker. (*c*) Patient in coma. Note slow rate and inverted *P*2 and 3, probably due to shifting of pacemaker in sino-auricular node.

The above factors give us some indication of how the heart may be affected by this treatment. It should be remembered that the changes are but one of the manifestations of the severe strain borne by the heart during hypoglycemic coma. Other complications, *e. g.*,

pulmonary edema, also have been recently recorded in the literature[3,18] and have been observed by us. In view of the increasing popularity of this method of therapy, one should bear in mind the possibility of complications particularly involving the cardiovascular system.

Conclusions. 1. The electrocardiographic alterations during 58 shock treatments on 40 different patients during the hypoglycemic shock treatment of schizophrenia have been recorded.

2. Noteworthy electrocardiographic changes were obtained in two-thirds of the shock treatments. These consisted of depression of the *ST* segments, diminution of the height of the *T* wave, prolongation of the *QT* interval, auricular fibrillation, auricular extrasystoles, shifting pacemaker, sinus arrhythmia and sino-auricular heart-block.

3. The profound changes in the organism during hypoglycemic shock and its relation to the electrocardiographic changes are discussed.

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145 units insulin at 7:30 A.M., 12 7:37. (*b*) 11:34 A.M. in coma, blood sugar 50 mg. %. Note slow rate and inverted *P*2 and 3, probably 50 per minute, and shifting pacemaker. (*c*) Patient in coma. Note slow rate and inverted *P*2 and 3, probably due to shifting of pacemaker in sino-auricular node.

FECAL IMPACTION.

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Fecal impaction is a common cause of symptoms resembling those of rectal and intestinal disease. The subject has received all too little attention in medical literature. The condition occurs following the use of barium for roentgenologic examination of the

gastro-intestinal tract, in cases of psychosis and not infrequently among multiparous women with relaxed perineal structures. It may also occur in the loop of bowel below the site of a double-barreled colostomy that has been performed for some obstructive lesion of the lower part of the intestine. Roughage, such as bran, psyllium seed, or unusually rough food eaten in time of need or on some other unusual occasion, often causes impaction.

The symptoms of fecal impaction are variable. A common one is the frequent passage of small liquid stools associated with great difficulty of control, a condition compared to urinary retention with overflow, by Cruveilhier.[3,4] This has not infrequently suggested "colitis" to a physician and in some cases the patients have been treated for colitis before a careful examination was made. The hard mass may produce bleeding. A non-productive urge to defecate is frequent. Enemas are often non-effectual. Constipation may alternate with apparent diarrhea. Gant[5] listed the following symptoms as associated with this condition: "nervousness, despondency, restlessness, muddy complexion, bad breath, indigestion, barking cough, morning vomiting, cold feet, night sweats, thirst, anorexia, dizziness, albuminuria, seminal emission, frequent micturition, sphincter spasms, depression, introversion, temporary mania, sense of weight and fullness, bearing down pains." All these symptoms are undoubtedly possible but unusual and only some of them will occur in any given case of fecal impaction. The diagnosis is usually dependent on one simple examination, that is, digital examination of the rectum.

Fecal impactions in the ampulla of the rectum are easily diagnosed by this examination. Those higher in the colon often can be felt through the abdominal wall. Their peculiar doughy feel, by palpation through the abdominal wall, is characteristic. Occasionally a hard mass will slide up the bowel lumen and elude the examining finger. Diagnostic errors are at times difficult to explain. A case reported by Buzzell[2,6] illustrates this. In this case the mass was thought to be a fetal head; involuntary micturition caused by pressure was mistaken for bursting of "the bag of waters."

The correct treatment cannot be overemphasized. It is usually simple. If possible, the mass may be broken up by digital manipulation at the time of the original examination. Hydrogen peroxide instilled into the rectum will help soften hard masses. It should be used diluted with water. Injection should be begun with a 1% solution. This may be increased to a 1.5% solution. Retention enemas of warm oil are useful and soothing and the peroxide enema should always be followed by an enema of oil that is left in the rectum as a retention enema. Small impactions may be softened with oil alone. After the impaction is removed, a regular bowel habit should be established. In Bushe's[1] publication in 1837, the following instruments were recommended for breaking up impactions: "blunt hooks, lever, gimlet, cutting forceps, narrow saw, lithotomy

forceps, a hammer and chisel, but above all, an intelligent boy with a small, well oiled hand."

The following cases are reported because they present some unusual features and because they came to our service in St. Mary's Hospital at the same time.

Case Reports. CASE 1.—A girl, aged 4, first came to The Mayo Clinic in July, 1927. She had been thrown against the foot pedals of an automobile and had sustained a severe perineal laceration. The laceration had been sutured by the family physician. She had been admitted to St. Mary's Hospital and treated for shock. In January, 1928, she returned complaining of fecal incontinence, which had been present since the accident and which had been associated with periodic constipation. At the time of her first admission in July, 1927, it had been impossible to recognize the anal sphincters. A plastic repair was attempted in January, 1928. She returned again in January, 1929, still complaining of fecal incontinence. A repair was again attempted but the extensive scarring made a good result doubtful. Thereafter her condition was rather satisfactory; she was able to predict bowel movements and had some control of defecation.

In the summer of 1937 she had further trouble, both in control and in obtaining a normal movement. Mineral oil seeped through without results. By the spring of 1938 enemas had become ineffectual. A mass was noted in the left lower quadrant of the abdomen. She noticed heaviness and discomfort in the lower part of the abdomen. Bowel movements became liquid and unpredictable; she was forced to wear diapers constantly. Blood was noticed in the stool at intervals. Her appetite became poor; her weight dropped from 100 pounds (45.4 kg.) to 89 pounds (40.4 kg.).

When she was admitted to the hospital in August, 1937, physical examination revealed a thin pale child with an anxious expression. There was a doughy movable mass in the left side of the abdomen, which extended from the iliac fossa to the level of the umbilicus. The perineal body was paper thin. A mass of feces, continuous with the abdominal mass, projected from the anal orifice. The usual laboratory examinations did not reveal anything abnormal.

The patient received the so-called residue-free diet. During a period of 3 days the impaction was broken up by periodic, manual and digital manipulation; each manipulation was followed by the use of solution of hydrogen peroxide and saline enemas. The rectum and the large intestine were completely emptied. The abdominal mass disappeared. Her appetite and sense of well-being returned. A plastic repair of the anal sphincter was done.

When the patient returned for check-up 3 months after the operation, she was feeling very well and had practically normal control of defecation.

CASE 2.—A man, aged 31, who was a lawyer, came to the clinic in July, 1938. He had been troubled with constipation since childhood. His abdomen had always been prominent. Since the age of 15 he had taken daily enemas.

In 1932 he had noticed a mass in the left side of the abdomen. Since that time it slowly but steadily had increased in size and he had been troubled with flatulence, bloating and heartburn. At different times the mass had been variously diagnosed as an enlarged spleen, a retroperitoneal cyst and other types of tumor.

Physical examination disclosed good general nutrition. There was considerable flaring of the lower ribs. The abdomen was protuberant. In the left side of the abdomen there was a round mass, which was 15 cm. in diameter and freely movable. The mass could be dented on pressure through the abdominal wall (Fig. 1). Rectal examination and the usual laboratory examinations did not reveal any abnormality. Roentgenographic examination

of the abdomen demonstrated a large mass of what was taken to be a fecalith in the left upper quadrant.

FIG. 1.—Segment of megacolon with part of the fecalith in place.

FIG. 2.—Huge laminated gall stone, the basis of impaction in the descending colon.

The patient was given a so-called residue-free diet. Treatment with solution of hydrogen peroxide and saline irrigations was begun. Eserine salicylate was given after the enemas. On several occasions pitressin was given. This procedure was repeated twice daily for 5 days. The mass was reduced to a tenth of its original size. A resection of a portion of the colon, by

exteriorization by the clamp method, was done for a localized megacolon which contained a small hard fecalith. The patient's convalescence was satisfactory.

CASE 3.—A white woman, aged 69, came to the clinic in June, 1938. For many years she had been troubled with mild indigestion after eating fatty foods. In 1934 she had had a severe attack of pain in the right upper quadrant of the abdomen which had been accompanied by vomiting. There had not been any jaundice. Since that time the pain in the right side of the abdomen had recurred at intervals.

From January, 1938 to June, 1938, she had noticed intermittent constipation and soreness in the left lower quadrant of the abdomen. On June 26, 1938, complete intestinal obstruction had occurred after barium had been given by mouth. She came to the clinic June 30, 1938, in this condition. The obstruction was largely relieved by medical measures of decompression including enemas, residue-free diet, hot abdominal stupes, parenteral fluids, and duodenal lavage.

At operation a segment of descending colon, which was the site of marked inflammatory changes that were associated with obstruction, was removed by exteriorization and resection with the three-bladed clamp. A large mass of omentum was found fixed in the region of the gall-bladder. Three weeks later she was sent home for convalescence.

Ten weeks after the primary operation she returned for closure of the colonic stoma. For several weeks she had had a sense of fullness in the rectum but had passed only mucus or blood. Enemas had been ineffectual. Examination disclosed a very firm fecal impaction which was about the size of a grapefruit. Usual measures of removal were largely ineffectual, although the mass was reduced somewhat in size. Under intravenous anesthesia a hard cylindrical mass 2.5 by 10 cm. was extracted manually.

Barium was suspected as the cause of this fecalith but incision and chemical analysis showed that it was formed about a large cholesterol gall stone (Fig. 2).

Comment. Fecal impaction has received too little consideration. It may be the cause of intense suffering. The diagnosis is usually not difficult and the treatment is exceedingly satisfactory. Relieving the symptoms produced by a huge rectal impaction makes the patient very grateful. When the impaction has been present for some time and when its constituents are very hard, digital removal may be followed by local abrasion and some discomfort. The solution of hydrogen peroxide must be carefully employed. If it is too strong, a secondary proctitis may be produced and the treatment of this condition may require many days. The whole substance of the treatment consists in breaking up the impactions as gently as possible and handling the rectum afterward in the most gentle manner possible. Thus, the use of instillations of warm oil and soothing suppositories is of as much importance as the actual dislodging of the impaction.

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ON THE ORIGIN OF AMMONIA IN THE URINE UNDER NORMAL CIRCUMSTANCES AND IN KIDNEY DISEASE.

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The ammonia which is found in the urine has been shown by Benedict and Nash[1a] to be produced in the kidney itself. For this reason the urinary ammonia cannot be considered to be an excretory product. It must rather be regarded as a metabolite of the kidney. It is because of the production and elimination of ammonia, as well as on account of the ability of the kidney to produce a urine with a hydrogen-ion concentration varying from that of the blood, that the kidney is a main factor in the maintenance of the acid-base equilibrium.

Three possibilities have hitherto been investigated as to the source of the urinary ammonia. The first of these has been considered to be urea.[1b] The most convincing contribution pointing in this direction was made by Mann and Bollman.[4] Working with hepatectomized dogs, they found a progressive decrease in the urea of the blood and the urine. When the urea output became very low, the urinary ammonia diminished. Intravenous injection of urea at this stage caused a definite increase in the urinary ammonia.

The second, according to Krebs,[3] who worked with the Warburg method, is that ammonia is produced from amino acids. As urea formation takes place, not in the simple manner assumed by the older biochemists, but rather in a very complicated fashion, through the mediation of ornithine and related compounds, one is inclined to believe that ammonia may be produced by a reversal of this same process.

In the third place, Embden and his co-workers[2] have considered the formation of ammonia from adenosine-phosphoric acid as very probable. Since the excretory function of the kidney is a reversible colloidal process, similar or analogous in character to that of muscular contraction, the formation of ammonia in the kidney may occur by a process resembling this part of muscular chemistry.

In the present state of our knowledge, we can consider only the first two processes resulting in the formation of urinary ammonia; that from amino acids, and that from urea.

This work was done in an effort to determine the presence of these factors in individuals with renal diseases of various types and to see how, if at all, they differ from the normal.

Procedure. All individuals studied were in the hospital. The diet was fixed at a constant protein level (about $\frac{2}{3}$ gm. per kg. of body weight) and

fats and carbohydrates varied according to the individual's total caloric requirements. No medication was administered at any time during the study. The 24-hour urine specimens were preserved with toluene and kept on ice until examined.

In each individual the period of observation was 12 days; the first 4 were used as control, the next 4 for the administration of urea (15 gm. 3 times a day in fruit juice after meals), and the next 4 again for control.

The following determinations were made on each 24-hour specimen of urine: 1, volume; 2, specific gravity; 3, total nitrogen; 4, urea nitrogen; 5, ammonia nitrogen.

The total nitrogen was determined by the Kjeldahl method; the urea and ammonia nitrogen in some cases by urease and titration, in others by the permutit method.

A total of 24 individuals with advanced renal disease were studied in this fashion. All had evidence of marked functional impairment. A number of individuals with apparently normal kidneys were also studied.

The following 5 cases have been selected out of these to illustrate the principles involved and the type of material studied.

CASE 1.—B. B. Control. Rheumatic Heart Disease. Mitral Stenosis and Insufficiency. Blood Urea N 15.6.

1936.	Volume.	Sp. gr.	Total N.	Urea N.	NH_3 N.	Chlorides.	Total base.	Diet: Cal. 1500; CHO 200, P 40, F 70.
3/14–15	260	1.027	3.77	3.27	0.43	1.19	27.1	
3/15–16	330	1.024	4.19	3.70	0.29	2.15	39.0	
3/16–17	240	1.028	3.87	2.49	0.47	1.90	23.2	
3/17–18	360	1.028	4.28	3.62	0.33	2.42	22.9	
3/18–19	860	1.022	16.77	15.40	0.77	3.53	77.4	Urea 45 gm.
3/19–20	1,020	1.020	21.32	19.93	0.61	2.45	54.8	" "
3/20–21	1,060	1.020	20.35	18.56	0.49	2.23	45.8	" "
3/21–22	1,090	1.026	23.76	20.05	0.83	1.85	44.9	" "
3/22–23	480	1.022	11.38	7.78	0.39	0.79	24.9	
3/24–25	310	1.020	4.65	3.59	0.52	1.48	47.4	
3/25–26	350	1.028	5.71	4.15	0.39	1.75	57.2	
3/26–27	310	1.026	4.40	3.14	0.59	1.40	50.8	

Comments: Control with no evidence of renal disease. Urinary ammonia doubled after administration of urea. Note the marked increase in output of urea when it was administered.

CASE 17.—M. S. Chronic Glomerulonephritis—Nephrotic State, Edema. 3/18/37: Blood Cholesterol 829; Protein 4.1; Alb. 1.6, Glob. 2.5.

1937.	Volume.	Sp. gr.	Total N.	Urea N.	NH_3 N.	Diet: Cal. 2060; CHO 300; F 60.
7/23–24	750	1.018	6.90	3.90	0.68	
7/24–25	790	1.017	7.05	3.86	0.77	
7/25–26	1,130	1.014	8.16	4.84	0.80	
7/26–27	745	1.018	5.81	3.43	0.78	
7/27–28	1,690	1.013	15.55	10.41	0.98	Urea 45 gm.
7/28–29	1,570	1.013	17.00	14.32	0.91	" "
7/29–30	3,020	1.014	32.07	24.96	0.80	" "
7/30–31	3,000	1.014	28.38	24.15	1.05	" "
7/31–8/1	1,750	1.013	18.22	16.91	0.63	
8/1–2	720	1.015	7.19	4.20	0.43	
8/2–3	1,350	1.016	11.87	8.94	1.00	
8/3–4	1,270	1.016	11.99	9.94	0.37	

Comments: This patient shows a normal response in his ammonia output; it is fairly high, and increased after urea. Output of urea is delayed.

CASE 14.—R. I. Adm. 12/29/36. Chronic Glomerulonephritis, Asthenic, Anemic. Urine: R.B.C. plus Albumin. 1/6/37: Urea (blood) 75.9. 2/10/37: Urea (blood) 64.9.

1937.	Volume.	Sp. gr.	Total N.	Urea N.	NH_3 N.	Diet: Cal. 1500; P. 50; CHO 230; F 30.
2/23–24	1,730	1.013	7.02	4.65	0.33	
2/24–25	2,920	1.008	9.46	7.45	0.20	
2/26–27	..	..	..	..	..	Specimen lost
2/27–28	1,820	1.012	9.34	7.12	0.40	Urea 45 gm.
2/28–3/1	2,540	1.011	12.14	9.70	0.31	" "
3/1–2	2,910	1.010	12.60	9.34	0.35	" "
3/2–3	3,340	1.009	15.83	12.99	0.30	" "
3/3–4	3,000	1.010	12.93	10.71	0.21	
3/4–5	1,800	1.011	8.87	7.22	0.29	

Comments: The urinary ammonia is fairly high, but is unaffected by the administration of urea. The diuresis is only moderate and the excess urea is eliminated very slowly.

CASE 5.—R. M., 21. Chronic Glomerulonephritis, Nephrotic Syndrome, Left Pleural Effusion. 9/14/35: Blood Urea N 21.6. 9/27/35: Blood Urea N 16.0.

1935.	Volume.	Sp. gr.	Total N.	Urea N.	NH_3 N.	Diet: Cal. 1500; P 45; CHO 200; F 60.
9/16–17	480	1.020	4.64	2.54	0.09	
9/17–18	340	1.024	4.76	2.25	0.08	
9/18–19	580	1.020	5.10	3.95	0.08	
9/19–20	640	1.017	6.77	3.81	0.06	
9/20–21	1,480	1.015	13.99	11.90	0.12	Urea 45 gm.
9/21–22	1,130	1.017	17.49	9.68	0.51	" "
9/22–23	1,800	1.014	19.69	16.78	1.06	" "
9/23–24	1,150	1.012	18.10	10.83	0.05	" "
9/24–25	610	1.014	8.80	5.85	0.03	
9/25–26	810	1.015	13.92	5.00	0.04	
9/26–27	980	1.015	12.81	6.28	0.03	
9/27–28	750	1.014	7.52	5.00	0.04	

Comments: This patient was apparently unable to produce urinary ammonia on a limited nitrogenous intake, but the administration of urea produced a considerable increase in the excretion of NH_3, which, however, became rapidly exhausted. A good diuresis was produced at the same time, and the urea output increased considerably. If we remember that there was about 80 gm. of nitrogen additional in the urea administered, we can see that only about one-half was excreted during the 4-day period and that urea was increased in the urine for days beyond that.

CASE 3.—I. D. Acute Hemorrhagic Glomerulonephritis; Uremia; Thrombocytopenic Purpura; Multiple Hemorrhages Throughout Body; Coronary Thrombosis; Gastric Ulcer; Cholelithiasis. Blood Urea N: 7/19/35, 59.7; 7/31/35, 37.3; 8/12/35, 39.3; 8/28/35, 91.8.

1935.	Volume.	Sp. gr.	Total N.	Urea N.	NH_3 N.	Diet: 1500 Cal.; P. 30.
7/30–31	940	1.014	8.55	4.94	0.06	
7/31–8/1	820	1.014	8.14	5.09	0.10	
8/1–2	1,080	1.014	8.65	5.65	0.07	
8/2–3	830	1.014	8.30	5.35	0.08	
8/3–4	1,630	1.014	14.52	9.93	0.11	Urea 45 gm.
8/4–5	1,780	1.012	17.52	14.08	0.07	" "
8/5–6	1,620	1.012	18.05	13.18	0.06	" "
8/6–7	1,600	1.013	15.86	13.22	0.05	" "
8/7–8	1,800	1.008	14.92	13.47	0.04	
8/8–9	1,330	1.012	16.08	8.37	0.05	
8/9–10	1,200	1.012	11.62	6.67	0.04	
8/10–11	920	1.010	9.38	4.30	0.03	

Comments: The administration of urea caused a mild diuresis with increased urea excretion, but by no means sufficient to determine the increased intake. Urinary ammonia remained persistently low during the entire period of observation. This individual showed advanced renal disease with very slight ability to form ammonia from either the diet or administered urea.

Comment. The amount of ammonia excreted in the urine depends upon a number of factors. First, there is the amount of strong acid produced in the intermediary metabolism or introduced into the system. Second, it depends upon the ability of the organism to form ammonia from its parent substances. Furthermore, there must be considered ammonia salts administered for experimental or for therapeutic purposes.

Normally, strong acids are preferably produced from proteins. Sulphuric acid, the strongest, arises from the oxidation of the sulphur derived from proteins. Its excretion through the kidneys invariably requires an equivalent amount of base, thus endangering the stock of alkali of the blood and tissues.

Phosphoric acid, though not as strong as sulphuric, usually exceeds it in quantity. It originates from various phosphoric esters, and is excreted both as an acid salt and as a basic salt, the latter carrying away twice as much base as the former.

Weak acids are excreted totally or partly as such, depending on their degree of dissociation, thus sparing base.

The production of ammonia, and of ammonia salts, prevents the loss of valuable fixed alkali. Under normal circumstances, therefore, the level of ammonia in the urine is commensurate with that of the protein metabolism, and is parallel to the oxidation of sulphur, that is, the formation of sulphuric acid.

Nevertheless, if the presence of ammonia in the urine were due exclusively to the task of maintaining the acid-base equilibrium, it should be missing in alkaline urine. Alkaline urine occurs under a variety of circumstances. It is produced by an intake of alkali in excess of the intermediary acid formation. It occurs in order to compensate for loss of acid in the gastric juice during the period of secretory activity of the stomach. Finally, in "pure" phosphaturia or alkalinuria, we find alkalinity of the urine without any of the above factors, due to some disorder of the autonomic nervous system, and probably to the temporary inability of the kidney to produce an acid urine. In such instances, in spite of the alkaline reaction, the kidney continues to produce ammonia, sometimes on a larger scale than normal. Apparently, therefore, a fraction of the urinary ammonia is formed, regardless of the renal mechanism responsible for the maintenance of the acid-base equilibrium.

Ammonia, though a base, and though of great importance in the formation of amino acids and in the chemistry of muscular contraction, is physiologically absolutely different from the fixed bases. It is present, if at all, in the blood and in the tissues in exceedingly small quantities, and thus it plays no direct rôle in the acid-base equilibrium. The small figure for milligrams per cent of ammonia obtained in the chemical analysis of the blood does not rise in the acidosis produced by the introduction or by the increased formation of acids. Of course, it is well known that ammonia is continuously

produced on a large scale from the amino acids, but it disappears at the same rate.

In normal individuals the urea output in the urine will vary considerably. Under certain circumstances, chiefly when the intake of nitrogen is limited, this output may be considerably reduced (B. B., Case 1). It is to be noted, however, that the urinary ammonia ranged well above 0.30 gm. of nitrogen per day, and that with the administration of urea the output of ammonia rose considerably.

With severe renal damage, this mechanism was found to be altered.

Results in Kidney Disease.—*Group I.* Some (M. S., Case 17) showed essentially a normal response. The ammonia output was good and it was increased by the oral administration of urea. It is interesting to note that the cases falling into this group differed clinically. One was an individual with polycystic kidneys and only slight urea retention in the blood (25 mg. %). Another was a boy with glomerulonephritis and a blood urea nitrogen of 80, apparently much more serious impairment of renal function. The case illustrated was a young man of 27 with a nephrotic picture (blood cholesterol 829; albumin 1.6; globulin 2.5; urea 18.1). These patients usually showed considerable delay in the excretion of ingested urea.

Group II. Others showed an output of ammonia corresponding to the nitrogenous intake, but the ingestion of urea in fairly large doses was followed by either a temporary, rapidly exhausted increase in the excretion of ammonia (R. I., Case 14) or no increase at all.

Group III. Other patients were apparently unable to produce urinary ammonia in an amount corresponding to the nitrogen intake, but could form ammonia when urea was administered (R. M., Case 5).

Group IV. Still others showed persistently only small traces of ammonia in the urine, not increased by the intake of urea (I. D., Case 3).

The diuretic effect of the urea certainly did not depend on the formation of ammonia, because there could be shown no relation between the diuresis and the excretion of urea on one hand, and the excretion of ammonia on the other.

In kidney disease there were all combinations of impairment and non-impairment of the two mechanisms of ammonia formation.

The following table summarized our 24 cases of renal disease:

Group I.	A+ U+*	6 cases
Group II.	A+ U−	9 cases
Group III.	A− U+	4 cases
Group IV.	A− U−	5 cases
		24 cases

* + = present. − = absent. A = formation basically from amino acids U = formation from urea.

These observations seem to point to the fact that ammonia formation from urea represents a particular index of kidney function, while the formation of ammonia from other precursors, is another.

The fact that some of these individuals (notably F. B., Case 13, not illustrated) possessed good ammonia formation in the kidney in spite of a very high blood urea, merely indicates that the various impairments of renal function, though frequently parallel, are not necessarily so; so that some kidneys, though unable to excrete sufficient urea, can still produce ammonia.

If the kidneys are functioning properly, increased output of ammonia results in the sparing of the base. If this cannot occur, the absence of ammonia formation tends to lead to a wasting of fixed base, a diminution of alkali reserve and sooner or later, acidosis.

Summary and Conclusions. Studies were made on individuals with normal kidneys and on those with renal disease in an attempt to clarify the mechanisms by which ammonia is produced in the urine and the rôle it plays in the maintenance of the alkali reserve.

On 24 individuals kept on constant nitrogenous intake, the urinary nitrogen output was studied before and after the administration of urea. Five of these cases were selected as illustrations.

It was found that there are at least two ways in which ammonia is produced in the urine, from urea, and from other precursors (most likely amino acids); and that these two mechanisms are not necessarily related; that ammonia formation from urea represents one index of renal function and that formation from amino acids represents another. Normally, this all occurs in the kidney.

Individuals with renal disease do not necessarily lose these two powers at the same rate; one mechanism may be preserved when the other has been lost. A certain margin of safety thus tends to be maintained, and the ability to produce some ammonia and thus spare some fixed base is retained for a long time.

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CHROMIUM POISONING IN INFANCY.

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A survey of the literature shows that not much is known definitely about the systemic effects of poisoning by chromium. The soluble salts of chromium are irritants to skin and mucous membranes

to such an extent that not much systemic absorption is liable to occur. In those cases in which absorption has occurred, as shown by the presence of chromium in excretions, the symptoms have suggested that the effect was chiefly upon the nervous system although, so far as we can discover, no neuropathologic studies have been made in such cases. We have had the opportunity to study, clinically, a case of chromium poisoning in an infant which presents features of great importance not only to physicians but also to toxicologists.

Case Report. The patient was a female, aged 14 months, the only child of healthy parents, and with no history of epilepsy on either side. She was delivered by Cesarean section and aside from a moderate feeding difficulty at first, she had been in good health. Her mental development was normal.

On August 28, 1938, she seemed rather dull and inactive, and appeared to have a slight fever. At 4 A.M. of August 29, she had her first convulsion, which was generalized. Following this she remained in a stupor and began having a series of convulsions at irregular intervals, which sometimes involved the right side of the body, sometimes the left, and at other times only one part, such as one side of the face or a leg.

She was seen by one of us at that time (J. F. S.) who found the rectal temperature 103°. There was no rigidity of the neck. The pupils were dilated but reacted to light. The ears were negative but the throat appeared to be inflamed. There was a soft systolic murmur at the base of the heart. The lungs were clear, and the abdomen negative. There was no diarrhea but there was mucus in the stools. The convulsions were treated with a sedative and the patient removed to a hospital. She remained unconscious and continued to have convulsions. Repeated examinations showed no change in her condition.

On August 31, it was noted that the pupils were dilated, responded sluggishly to light, and at times there was a divergent strabismus. The ocular fundi were negative. There was no paralysis of the face, tongue, or extremities, and no disturbance in muscle tone. The tendon reflexes were normal and equal on each side. The plantar reflexes were normal. There was no Kernig's sign and no Brudzinski sign. During the course of the examination the patient had several attacks, one involved the right side of the face, and another the left leg. They lasted about a minute and the movements resembled those of Jacksonian epilepsy. Although apparently unconscious, she would occasionally cry out. A few râles were heard in the lungs but a Roentgen ray examination of the lungs was negative. There was a faint systolic murmur at the base of the heart.

The urine was straw colored, cloudy, and with acid reaction. It contained a trace of albumin but no sugar, and on September 3, 1938, no albumin but a trace of sugar. Subsequent tests up to October 3, 1938, were negative. There were no casts at any time. The first blood examination showed 3,500,000 red blood cells, 16,300 leukocytes with a hemoglobin of 70%. The neutrophils were basophilic but there was no basophilic stippling of the red blood cells. The Kahn test on the blood was negative and the blood N. P. N. was 31.9 mg. %. The blood and leukocyte counts, repeated daily, gradually returned to normal.

A spinal puncture was done Sept. 1, 1938. The cell count was not increased. Pandy's reagent gave a positive reaction but the test with ammonium sulphate was negative. The total protein was 16. The gold sol. 001100000. The Kahn test was negative.

The clinical history and findings suggested an encephalitis, either of toxic or infectious origin. A lead encephalopathy in an infant would cause somewhat similar, though not identical, symptoms. One week previous to the onset of the trouble the child was seen eating the paint from a souvenir tray. The father said that the paint had been daubed on thickly and that he had been able to remove some of the material from the patient's mouth at the time.

The urine was examined in the State Laboratory at Lansing, on Sept. 1, 1938, for lead, chromium, and mercury, but only chromium was found. This was repeated on Sept. 2, with the same result. On Sept. 12, 16, and 23, no chromium was found. The feces showed none on Sept. 1, but a trace of chromium was found in Sept. 2, and none on Sept. 19.

The chemist reported that the paint material was a silicate with the pigment an insoluble chromite ore.

The child was treated with sedatives as necessary, intravenous Ringer's solution, and was given 2 blood transfusions. Syrup of the iodide of iron was given by mouth when possible. Magnesium sulphate enemas were given daily. The temperature returned to normal on Sept. 4, and convulsive seizures stopped on the 7th day, but following this she began having choreiform movements. These subsided gradually and the patient continued to improve, although still in a semi-stupor at the end of 6 weeks. Her improvement was slow and in March, 1939, she was just beginning to creep. She could balance in sitting. She could definitely see, hear, smell, and taste. Her reflexes were normal, and the ocular fundi were normal. There was no paralysis.

A search of the literature shows that this case is important in several ways and in some respects, unique. Practically all of the cases of systemic chromium poisoning that have been reported have resulted from taking potassium bichromate, usually in solution. In some industries the inhalation of chromium dust may cause ulceration of the mucous membrane of the nose, and those who may immerse the hands in chromate solutions, photographers for instance, may develop excoriations of the skin, the so-called "chrome holes," but usually there are no systemic effects in such cases. Bichromate is a powerful irritant to the stomach so that the patient vomits and not much is absorbed although in a case reported by Jonssen where the patient drank a 5% solution of potassium bichromate, painful convulsions of the arms and legs came on after 6 hours. In the case reported by Goldman and Karotkin[1] the temperature went up to 101°. This case and the one we report, are the only cases in which chromium was recovered from the urine, but in neither one was there definite evidence of nephritis. Fever in chromium poisoning is not unusual. In our case, the temperature of 103° F. was higher than in other reported cases but the fact that it was a rectal temperature in an infant might account for this difference. The dilated pupils which was rather a striking feature in our case, is a common symptom of chromium poisoning.[2]

Poisoning by chromium is not common. Goldman and Karotkin could find only 69 cases in the literature. In our search we have found no other case of chromium poisoning in an infant. Nor have we been able to find a case in which the poison gave only a slow

acting systemic effect without gastro-intestinal symptoms. We believe that the chromium in this case was not absorbed into the system until the chromium-containing material had been acted upon by some substance in the gastro-intestinal tract, probably liberating the chromium gradually.

Summary. A case is reported of chromium poisoning in an infant due to the ingestion of a paint containing a relatively insoluble chromium compound. There was no evidence of local gastro-intestinal irritation. The symptoms were systemic and showed evidence of the effect on the nervous system. The most important symptoms were convulsions, stupor, dilated pupils, negative neurologic findings, and normal spinal fluid. Chromium was found in the urine and feces.

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BOOK REVIEWS AND NOTICES

IMMUNITY PRINCIPLES AND APPLICATION IN MEDICINE AND PUBLIC HEALTH. An Exposition of the Biological Phenomena of Infection and Recovery of the Animal Body from Infectious Disease, with Consideration of the Application of the Principles of Immunity to Diagnosis, Treatment, and Prophylaxis and Their Usefulness in the Control of Epidemics. By HANS ZINSSER, M.D., Professor of Bacteriology and Immunology, Harvard Medical School, JOHN F. ENDERS, PH.D., Assistant Professor of Bacteriology and Immunology, Harvard Medical School, and LEROY D. FOTHERGILL, M.D., Assistant Professor of Bacteriology and Immunology and Associate in Pediatrics, Harvard Medical School. Pp. 801. Fifth edition of "Resistance to Infectious Diseases." New York: The Macmillan Company, 1939. Price, $6.50.

THE aim of the present edition is clearly stated by the authors as representing an endeavor to meet the need for increased correlation between its principles as revealed in the laboratories and their application to the problems of the clinic and of public health. "The most notable advances of recent years in this subject (immunology) have resulted from intimate collaboration of the bacteriologist and the chemist on the one hand, and the bacteriologist and clinician on the other." Much of the older material has been eliminated to make room for the newer knowledge. The book is conveniently divided into two parts, *i. e.*, principles and theory, and the application of immunological knowledge to medicine and public health. Throughout, both the interdependence of theory and practice has been stressed, thus "the laboratory worker, turning to the practical sections, may derive stimulus from the recognition that many of the principles at first conceived without obvious possibility of applied value have ultimately served to enrich diagnosis, prevention or therapy; and the practitioner, referring to Section II for details of specific procedures, can turn back to the chapter on principles and there find discussions which will aid him more fully to understand the observations and reasoning upon which many of the methods used in practice are based." The reader will find that the aims of the writers have indeed been fulfilled. B. L.

AN INTRODUCTORY GUIDE TO BIOCHEMISTRY. By SIDNEY BLISS, PH.D., Professor of Biochemistry, Tulane University School of Medicine. Pp. 103. Philadelphia, W. B. Saunders Company, 1939. Price, $1.25.

ACCORDING to the author the purpose of this brief outline is to give to the prospective student of biologic chemistry a general idea of the subject as a whole before beginning a detailed study of the various subjects concerned. As such it might be of some practical value. However, it is difficult to see what type of student the author had in mind in selecting the material. For example, the statement is made that a base is the chemical opposite of an acid, and again unsaturation in organic compounds is explained, apparently assuming no knowledge of either inorganic or organic chemistry on the part of the student. In contrast to this, in discussing physiologic oxidation of fats, it is stated that oxidation takes place on the beta carbon atom without further explaining which carbon atom is so

labeled. Some definitions, such as that a fat is a salt of the organic base glycerol, could also be questioned.

In spite of these criticisms the author has succeeded in outlining the field of physiologic chemistry in a very few pages, and although it is not written essentially for the layman, a knowledge of neither chemistry nor physiology would be necessary to understand and enjoy this simple treatise.

J. J.

THE FORM AND FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM. An Introduction to the Study of Nervous Diseases. By FREDERICK TILNEY, M.D., PH.D., Director Emeritus, Neurological Institute, New York, and HENRY ALSOP RILEY, M.D., Director and Attending Neurologist, West Service, Neurological Institute; Professor of Neurology and Neuroanatomy, Columbia University, College of Physicians and Surgeons, New York. Foreword by the Late GEORGE S. HUNTINGTON, SC.D., M.D. Pp. 851; 600 illustrations. Third edition. New York: Paul B. Hoeber, Inc., 1938. Price, $10.00.

THIS new edition of a well-known book reflects the advances of our knowledge in the field of neurology. While the basic plan of the earlier editions has been retained, many sections have been rewritten to present current views. This is especially true of the discussion of the cerebellum, the cerebral cortex, the interstitial tissue, the hypothalamic region, the hypophysis and the epiphysis. Despite the addition of much new material, the bulk of the former volumes has been reduced by judicious condensation and by the elimination of detail of interest mainly to the comparative anatomist. Like the two previous editions, the present work represents ripe scholarship and adequately fulfills the aim of the distinguished authors: to correlate form and function, and, by the extensive citation of actual cases, bridge the gap between neuroanatomy, neurophysiology and clinical neurology.

B. L.

THE MEDICAL CLINICS OF NORTH AMERICA. VOL. 23, NO. 3 (NEW YORK NUMBER, MAY, 1939). Pp. 277; 30 illustrations. Philadelphia: W. B. Saunders Company, 1939.

OF the 22 articles in this number, 15 are included in the symposium on pediatrics, each on a different phase—nosology, prognosis and especially treatment. The remaining articles treat such topics as lipoidosis, pellagra, vitamin deficiencies, flaccid paraplegias and the shock treatment of psychosis. One is mildly surprised to meet Senator's antiquated term "autointoxication of intestinal origin," and still more so when one reads further that the diagnosis must be based, not on laboratory studies, but "largely" upon clinical impressions. Doubtless colonic irrigations will help many cases diagnosed in this way.

E. K.

HYPERTENSION AND NEPHRITIS. By ARTHUR M. FISHBERG, M.D., Associate in Medicine, Mount Sinai Hospital, New York City. Pp. 779; 40 illustrations and 1 colored plate. Fourth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, $7.50.

THE rapid progress in the clinical and experimental investigation of Bright's disease has necessitated a complete revision of this work. The following are but a few of the new subjects discussed, and of old sections rewritten: Goldblatt's work on hypertension, Masugi's experimental production of glomerulonephritis, the Addis count, Cushing's syndrome, nature and treatment of the toxemia of pregnancy, hemoglobinuric nephrosis;

papilledema in hypertension; mercurial diuretics, etc. Simple laboratory tests, such as can be performed by any practitioner, are fully described. It is emphasized that the more elaborate laboratory procedures are needed in only a minority of patients. The book is an excellent guide, and rightly deserves the popularity it has long enoyed. B. L.

LABORATORY MANUAL OF THE MASSACHUSETTS GENERAL HOSPITAL. By FRANCIS T. HUNTER, M.D. Pp. 119. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, $1.75.

SINCE the second edition of this booklet more than 10 years ago, diagnostic, prophylactic and minor therapeutic procedures have been greatly modified and developed. This progress is faithfully reflected in the present edition. In some cases obsolescent procedures are retained, apparently on the principle of being sure that you are on with the new love before you are off with the old. This booklet continues to be one of the best of its kind. E. K.

RICHTLINIEN PRAKTISCHER ORTHOPÄDIE. By DR. ALBERT LORENZ. Pp. 464; 123 illustrations. Wien: Franz Deuticke, 1939. Price, Paper, M. 15; Bound, M. 16.80.

THIS work, as the author indicates, is intended for the orthopedic specialist rather than for the medical student or general practitioner. Description of material which would be of importance to the latter is generally sketchy and most of the treatise deals with technical detail as to therapy, both operative and non-operative.

Much of this book was written while the author was in New York and admittedly he has paid a great deal of attention to the English and American literature. This work is divided into 35 chapters, dealing with plaster bandaging, physiotherapy, anesthesia, flat feet, arthritis deformans, tuberculosis of bones and joints, various congenital deformities, such as wry neck, club feet, Sprengles deformity and congenital dislocation of the hip. There are also chapters on spastic paralysis, infantile paralysis and the muscle dystrophies.

In the field of fractures mention is made only of the fracture of the neck of the femur. In this chapter in addition to presentation of the Whitman abduction and the nailing method, the author has included an operative procedure of his own, which in the Reviewer's opinion, is possibly of value in certain chosen cases.

Unfortunately, there is no mention either of bone deforming conditions such as arthritis deformans or hyperparathyroid states (osteitis fibrosa cystica) nor is any space allotted to tumors.

Of particular interest is the detailed chapter on congenital dislocation of the hip, in which much discussion is allotted to the bloodless and to the operation treatment. The author believes in relatively prolonged fixation in plaster after bloodless reduction and differs from one American authority in a very naive fashion. This latter orthopedic surgeon frankly states that his experience proves bloodless reduction a failure if it is not satisfactory after four months of immobilization in plaster. The author says, that with that opinion he disagrees, but in "rich America, time is money."

In his introduction the author goes into some detail about the question of congenital deformities and makes the statement that eradication of such deformities might well be attained by the process of voluntary sterilization. One might see eye to eye with him regarding certain hereditary conditions, but the exact logic of this applied to congenital deformities is

a bit obscure. Possibly, into medicine, too, has crept some of the new German ideology.

In general, however, the book is a good one and both of interest and value to those orthopedic surgeons who are familiar with German and, though lacking in some aspects as in fractures, though mirroring to a large degree the author's opinions. It is of good interest and value for those orthopedic surgeons who are familar with German. I. S.

IT'S MORE FUN TO BE THIN. By JEAN Z. OWEN. Pp. 182; illustrated. Boston: Marshall Jones Co., 1939. Price, $2.00.

IN most books and magazine articles written with the purpose of helping those in need of advice in regard to reducing, diet and exercise are stressed and outlined in a matter of fact way, like a doctor's prescription, but the author of "It's More Fun to be Thin," has made an enjoyable game of this endurance test. In this very delightful and entertaining book, she has demonstrated, by a series of case histories, that it is much to a woman's advantage in every way to keep her figure trim. The rules of the game are well-planned diet, exercise, an interest in things other than food and, if needed, the supervision of a physician. While this book is written in a gay refreshing style, the contents are entirely accurate and reliable. This book should be welcome to doctors to recommend to their obese women patients. M. S.

RURAL MEDICINE. Proceedings of the Conference held at Cooperstown, New York, October 7 and 8, 1938. Pp. 268; 15 illustrations, 13 tables and 35 charts. Springfield, Ill.: Charles C Thomas, 1939. Price, $3.50.

THIS book presents the papers read and discussed at a conference on Rural Medicine organized by the staff of the Mary Imogene Bassett Hospital of Cooperstown. The purposes of the conference were as follows: 1. To provide a forum for discussion of problems of rural medicine and to give publicity to ideas and suggestions for accelerating progress in rural hygiene. 2. To define and set apart as distinct problems those which have a special relationship to the health of rural communities. 3. To present a true picture of rural morbidity, as far as the experience of a single rural hospital may serve for this purpose. 4. To stimulate unsentimental scientific scrutiny of those conditions which influence the incidence of disease and disability in rural populations and to apply such scrutiny to the problems of rural medicine.

The conference brought together a noteworthy gathering of experts on public health, medical education, organization of medical service and rural life. It held four sessions, devoted respectively to rural morbidity, health department programs and school health programs in rural areas, postgraduate medical education in rural areas and economics of rural medicine. At these sessions, papers were presented by members of the staff of the Bassett Hospital, by local physicians, by biostatisticians who had studied the local community and by experts on the various topics discussed. The volume contains 16 papers and the excellent discussions which they evoked, and is concluded by an extensive bibliography of Rural Medicine.

This collection of papers raises many questions regarding Rural Medicine and answers conclusively but a few of them. It demonstrates clearly, however, that plans for the improvement of medical service must be adaptable to local needs and must have sufficient flexibility to meet many variations in local conditions and attitudes in order to be effective. The problems of rural medicine are set forth from a variety of aspects, and those interested

in the changing conditions of medical care should study this excellent approach to the subject which this book represents, namely an effort to study at first hand and at close range one phase of the problem of medical service by a distinguished group of leaders in public health and medical service.

The discussion of economics of rural medicine is noteworthy. Beginning with accounts of experience in this field, the discussion is continued by close observations and sensible interpretations of the local situation followed by a broad general discussion both from a liberal and from a more conservative point of view.

The conference reported in this book is an excellent example of the educational process which is essential, if intelligent coöperation is to be effected between the public and the medical profession, in working out the details of any program of medical service which may be advanced by legislation. Dr. George Mackenzie and his colleagues of the Mary Imogene Bassett Hospital deserve much credit for inaugurating such a valuable method of stimulating sound thinking based on facts, which is especially valuable at this time of controversy regarding medical service. G. R.

A Textbook of Orthopaedic Nursing. By Evelyn C. Pearce, Sister Tutor, The Middlesex Hospital. Foreword by the Late Sir Robert Jones, Bart., K.B.E., C.B., F.R.C.S., and an Introductory Chapter by Dame Agnes Hunt, D.B.E., R.R.C., Founder and Honorary Superintendent, the Shropshire Orthopædic Hospital and Agnes Hunt Surgical Home, Oswestry. Pp. 230; 101 illustrations. Second Edition. London: Faber & Faber Ltd., 1939. Price, 7s. 6d.

The object of this book, the first textbook on Orthopædic Nursing ever written, according to the author is "to help nurses in training in the general hospitals of the country to a better understanding of the treatment of orthopædic cases and consequently to a deeper interest in this branch of surgical nursing." In the Introductory chapter written by Dame Agnes Hunt, founder of the Shropshire Orthopædic Hospital and Agnes Hunt Surgical Home, the object of Orthopædic work is stated as being that of Prevention, Treatment and Training. The importance of the nurse as a teacher in preventive measures is illustrated graphically by this nurse, who has had so much experience in this particular clinical field. Some points on the Anatomy of those structures involved in deformity and disease are described in the first chapter and then on to congenital deformities for which treatments are described clearly in the text and by photographs, drawings and Roentgen-ray photographs. The infectious diseases that so often result in deformities, such as acute anterior poliomyelitis, spastic paralysis (Little's disease), rickets and inflammatory disease of bone, including tuberculous arthritis, osteoarthritis, spondylitis and fibromyositis, have a chapter devoted to each, in which the disease is described as to etiology, common deformities occurring (with pictures showing typical conditions) and the treatment and nursing care. There is a chapter on deformities of the vertebral column with many illustrations showing every type occurring commonly and also positions assumed in exercises used to overcome these conditions. A chapter on injuries to bone and joint, fractures and dislocations and internal derangements of the knee joint describes many kinds of each of these conditions with treatments. The last chapter covers applications of splints and extensions, preparation of the skin before operations and application of plaster of Paris. Here not only by rules but by many photographs and drawings is shown the art of carrying out these procedures. This book should be in the library of every school of nursing as it contains so much material of interest to nurses in orthopædic work and to those who include this clinical field in their general field of nursing. M. S.

THE PATIENT AS A PERSON. A Study of the Social Aspects of Illness. By G. CANBY ROBINSON, M.D., LL.D., Sc.D., Lecturer in Medicine, Johns Hopkins University. Pp. 423. New York: The Commonwealth Fund, 1939. Price, $3.00.

WE have passed through a generation in which Chairs of Medicine were held by persons especially trained in pathology. This led to great interest in that kind of disease which could be demonstrated at necropsy, and a corresponding lack of interest in "functional" diseases. There has doubtless always been some protest against this trend. Medical Philadelphia still tells stories of patients whom Osler passed by with a wink, who went to Weir Mitchell and were cured. Later Peabody's book, "Doctor and Patient," attracted attention. Now comes Dr. Robinson with much documented evidence. He took 174 unselected patients admitted to the Johns Hopkins Hospital, gave them long interviews at the hospital, and followed them to their homes. He promptly discovered many important facts about which the hospital doctors were entirely ignorant, *e. g.*, in 66% adverse social conditions bore a definite relation to their illness. A common error on the part of the hospital doctor was that the patient's emotional disturbances were not given adequate consideration. Under such circumstances the time and money wasted in useless laboratory work and irrelevant studies must have reached no small total.

Dr. Robinson suggests a solution to these problems. He would have departments covering the social aspects of illness established in our scheme of medical education. Meanwhile, each third year student is assigned one out-patient to study, under supervision, as a total individual. After this study is complete the data are presented in a conference attended by public health administrators, medical social workers, psychiatrists, and so on.

Surely everyone familiar with the deficiencies of hospital practice will applaud the author's efforts to improve the handling of the large group of hospital patients incapacitated, in whole or in part, by the social maladjustments of our era. I. S.

STUDIES ON THE CHANGING INCIDENCE OF PEPTIC ULCER of the Stomach and Duodenum. By GUNNAR ALSTED, M.D., Privat-docent at the University of Copenhagen; Assistant Physician and Member of the Staff, Bispebjerg Hospital, Copenhagen. With a Preface by PROFESSOR E. MEULENGRACHT. Pp. 148; 12 illustrations. Copenhagen: Ejnar Munksgaard, 1939. Price, 10/-.

ALSTED believes that the incidence of peptic ulcer in the female sex has decreased during the past half century, while it has remained unchanged in the male. In the male, however, its location has shifted from the stomach to the duodenum and it has become more chronic. Its chronicity in men has led to a greater number of male hospital admissions for ulcer, and this together with the actually decreased incidence in women accounts for the altered sex relationship. His conclusions are based on an exhaustive analysis of statistical data, which some may feel are too limited; but certainly his arguments seem sound and they deserve further consideration. The book should be read by all interested in the subject. T. M.

ROENTGEN TECHNIQUE. By CLYDE MCNEILL, M.D., Louisville, Kentucky. Pp. 315; 268 illustrations. Springfield, Ill.: Charles C Thomas, 1939. Price, $5.00.

THE author's endeavor to reduce the contents of a large volume to a useful and practical reference book has been successful. The book is divided

into four parts: head, extremities, trunk and exposure technique. The standard Roentgen positions are dealt with in a systematic manner, each position being accorded 2 full pages. Photographic illustrations showing the tube, patient and casette appear on the left hand page while descriptive matter and technical factors appear on the right. The book is designed primarily for average equipment, and with this in mind, methods of pineal localization, interpedicular measurements and pelvimetry are included. Such recent advances as kymography and tomography are briefly described, and in places where the subject matter is inadequate, references have been added. The purpose of the book seems to be to bring the essential facts of technique together in a compact, handy manner. The author has eliminated the verbiage of the subject which he treats and held to generally accepted procedures. This book is recommended as a handbook to those interested in the basic facts of Roentgen technique. E. G.

MEDICAL VOCABULARY AND PHRASES. English, German, French, Italian, Spanish. By JOSEPH S. F. MARIE. Foreword by CHEVALIER JACKSON, M.D., Sc.D., LL.D., F.A.C.S., Honorary Professor of Broncho-Esophagology and Consultant in Broncho-Esophagologic Research, Temple University, School of Medicine, Philadelphia. Pp. 358. Philadelphia: P. Blakiston's Son & Co. Inc., 1939. Price, $3.00.

THE German, French, Italian and Spanish equivalents of some 7000 English medical terms, arranged in parallel columns for easy comparison. Also 9 pages of phrases prepared for use in conversation with nurses or patients. The potential value of such a book is obvious, and could well justify Dr. Jackson's enthusiastic foreword: "All my medical life I have wanted just such a book as this. It makes me sad to think of the thousands of weary hours it would have saved me, hours spent in handling a clumsy stack of dictionaries." Unfortunately, the value of the book is decidedly impaired by the large numbers of mistakes, nearly all of them in the German terms. A casual inspection of the first hundred pages disclosed 112 errors (more than 1 for every 25 English words): errors that are mostly the evidence of both unintelligent and careless proofreading, as when the word clavicle is variously translated in three places as "die Schlüsselbein," "das Schüsselbein," and "das Schlüsselbein." It is to be hoped that an early revision will produce what could be an excellent book. R. K.

FEVER THERAPY TECHNIQUE. By JACK R. EWALT, M.D., Resident Psychiatrist, Colorado Psychopathic Hospital; Instructor in Psychiatry, University of Colorado School of Medicine, Denver; ERNEST H. PARSONS, M.D., Captain, Medical Corps., United States Army; Neuropsychiatrist, Sternberg General Hospital, Manila, Philippine Islands; STAFFORD L. WARREN, M.D., Associate Professor of Medicine in Charge of Division of Radiology, University of Rochester School of Medicine, Rochester, N. Y., and STAFFORD L. OSBORNE, B.P.E., M.S., Associate in Physical Therapy, Northwestern University School of Medicine, Chicago. Foreword by FRANKLIN G. EBAUGH, M.D. Pp. 161; 16 illustrations. New York: Paul B. Hoeber, Inc., 1939. Price, $2.50.

A CONCISE accurate presentation of the various methods used to induce therapeutic fever. The authors have been particularly interested in mechanical devices, including the radiant energy cabinet, the hypertherm, and high frequency currents, so that the descriptions of these techniques are excellent. (One might differ, however, with their views as to some of the principles

underlying fever therapy and consequently their evaluation of non-specific protein shock treatment.) The book is considered by the authors as an adjunct to, not a substitute for, the post graduate instruction which they feel is necessary for the physician who wishes to administer fever therapy by any of the mechanical methods. R. K.

STUDIES FROM THE CENTER FOR RESEARCH IN CHILD HEALTH AND DEVELOPMENT, SCHOOL OF PUBLIC HEALTH, HARVARD UNIVERSITY. (Monograph of the Society for Research in Child Development, Vol. IV, No. 1, Serial No. 20.) I. The Center, the Group under Observation, Sources of Information and Studies in Progress. BY HAROLD C. STUART, M.D., and STAFF. Pp. 261; 66 illustrations. Washington, D. C.: Society for Research in Child Development National Research Council, 1939. Price, $1.75.

DR. STUART has presented a preliminary report of a very extensive investigation of child development which was begun in 1930. He describes the growth of the Center and gives details of the methods used and the conditions under which observations have been made. At the time of writing there is a personnel of 28 members, 8 of whom are physicians, which includes pediatricians, an obstetrician, an orthopedist, and specialists in roentgenology, psychology, anthropometry, nutrition and dentistry, as well as nurses, social service workers, technicians and secretaries.

The material under consideration consists of a normal child series in which 224 children are actively enrolled, a normal pregnancy series (1935-1937) in which 86 cases were studied, and a premature birth series (begun in 1934) which includes 47 children who are still being followed. The second half of the monograph is a detailed report on the studies of 2 sisters, each of whom has 3 children. The remarkably complete family analysis and the detailed nutrition studies are of especial interest.

This publication should be read by all those who will be interested in the subsequent reports from the Center. J. R.

TEXTBOOK OF PATHOLOGY. A CORRELATION OF CLINICAL OBSERVATIONS AND PATHOLOGICAL FINDINGS. By CHARLES W. DUVAL, Professor of Pathology and Bacteriology, Tulane University School of Medicine; Chief Visiting Pathologist, Charity Hospital, New Orleans, etc., and HERBERT J. SCHATTENBERG, M.D., Associate Professor of Pathology and Bacteriology, Tulane University School of Medicine; Visiting Pathologist, Charity Hospital, New Orleans. Pp. 681; 383 illustrations and 13 colored plates. New York: D. Appleton-Century Company, Inc., 1939. Price, $8.50.

IN a field already crowded with one-volume textbooks, new books on pathology continue to arrive periodically. The Duval and Schattenberg contribution aims to correlate clinical observations and pathologic findings, a viewpoint given modern emphasis in the several texts of Professor Boyd. This trend, carried to an almost incredible extreme by Smith and Gault, threatens to relegate the science of pathology forever into the mean and minor rôle of a lowly handmaiden to clinical medicine. It is discouraging to meet, on turning the first page, a faulty understanding of Menken's recent work on inflammation and an unbelievable misquotation of his term "leukotaxine" as "leukotoxine."

General pathology is dealt with in a cursory, often inexact and sometimes quite erroneous manner, as, for instance the description of hyaline degeneration as due to a "deposition in the tissues of a peculiar albuminous substance known as hyaline." The special pathology section offers nothing new and the correlations with clinical observations contain little more than is usually

given in descriptive pathology. The bibliography is brief and restricted entirely to publications in English. The book is plentifully provided with plates of mediocre quality.

With revised editions of such sound textbooks as Karsner's and MacCallum's available, the Reviewer cannot find anything in this new work which would lead him to recommend its presence in the library of student, physician or pathologist. D. C.

MAN AGAINST MICROBE. By JOSEPH W. BIGGER, Sc.D., M.D., F.R.C.P.I., M.R.C.P. (Lond.), Professor of Bacteriology and Preventive Medicine, Trinity College, University of Dublin. Pp. 304; 16 illustrations and 18 plates. New York: The Macmillan Co. Price, $2.50.

THE book is written for "a person of some education, but not a scientist" and should be very interesting to a layman. The author not only describes somewhat man's fight against microbes but also, in non-technical terms, briefly describes what microbes are, how they are studied by microbiologists, how they are identified and how man acquires his microbes. The author has obtained his material from authentic sources and this book could very profitably be included in reading lists for high school and college students. H. M

NEW BOOKS.

The Surgery of Pain. By RENÉ LERICHE, M.D. (LYON), LL.D. (GLASGOW), F.R.C.S. (ENG.), (HON. CAUSA), etc., Professor of Clinical Surgery, University of Strasbourg. Translated and Edited by ARCHIBALD YOUNG, B.Sc., M.B., C.M., F.R.F.P.S.G., F.A.C.S. (HON.), M.D. (STRASBOURG), (HON. CAUSA), etc., Regius Professor of Surgery, University of Glasgow; Visiting Surgeon, Western Infirmary, Glasgow. Pp. 512; 18 illustrations. Baltimore: The Williams & Wilkins Company (A William Wood Book), 1939. Price, $6.50.

The Journal of Endocrinology, Vol. 1, No. 1, June, 1939. A new journal to be devoted to the publication of papers on endocrinological subjects. Edited by E. C. DODDS. Assistant Editor: R. L. NOBLE. Editorial Board: P. M. F. BISHOP, C. R. HARRINGTON, G. F. MARRIAN, A. S. PARKES, F. G. YOUNG, S. ZUCKERMAN. Pp. 116; many illustrations. London and New York: Oxford University Press, 1939. Price, 10s. per copy (30s. per vol. or $6 in U. S.).

Perspectives in Biochemistry. Thirty-one Essays presented to Sir Frederick Gowland Hopkins by past and present members of his Laboratory. Edited by JOSEPH NEEDHAM and DAVID E. GREEN. Pp. 361; illustrated. Cambridge: At the University Press; New York: The Macmillan Company, 1939 (Fourth Impression). Price, $4.75.

Hay Fever, What to Do About It! By HARRY S. BERNTON, M.D., F.A.C.P., Clinical Specialist in Allergy Bureau of Chemistry and Soils, United States Department of Agriculture; Professor of Hygiene, School of Medicine, Georgetown University; Allergist to the Providence Hospital, Washington, D. C., etc. Pp. 76; illustrated. Washington, D. C.: Ransdell, Inc., 1939. Price, $1.00.

Not a treatise on hay fever, but useful information about certain aspects of hay fever for those afflicted with this disease. R. K.

Menstrual Disorders. Pathology, Diagnosis and Treatment. By C. FREDERIC FLUHMANN, B.A., M.D., C.M., Associate Professor of Obstetrics and Gynecology, Stanford University School of Medicine, San Francisco; Assistant Visiting Obstetrician and Gynecologist to Lane and Stanford University Hospitals, etc. Pp. 329; 119 illustrations. Philadelphia: W. B. Saunders Company, 1939. Price, $5.00.

Cardiovascular Diseases. Their Diagnosis and Treatment. By DAVID SCHERF, M.D., and LINN J. BOYD, M.D., F.A.C.P., Associate Professor of Clinical Medicine and Professor of Medicine, respectively, The New York Medical College, Flower and Fifth Avenue Hospitals. Pp. 458; 10 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, $6.25.

Pneumonia. With Special Reference to Pneumococcus Lobar Pneumonia. By RODERICK HEFFRON, M.D., Medical Associate, The Commonwealth Fund; Formerly Field Director, Pneumonia Study and Service, Massachusetts Department of Public Health. Pp. 1086; 18 figures, 181 tables and several maps. New York: The Commonwealth Fund, 1939. Price, $4.50.

Operative Orthopedics. By WILLIS C. CAMPBELL, M.D., Memphis, Tenn. Pp. 1154; 845 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, $12.50.

Peripheral Vascular Diseases. Diagnosis and Treatment. By WILLIAM S. COLLENS, B.S., M.D., Metabolist; Chief of the Clinic for Peripheral Vascular Disease; Chief of the Diabetic Clinic, Israel Zion Hospital, Brooklyn, etc., and NATHAN D. WILENSKY, M.D., Assistant in Clinic for Perivascular Diseases; Assistant in Diabetic Clinic, Israel Zion Hospital, etc. Pp. 243; 77 illustrations, and 3 color plates. Springfield, Ill.: Charles C Thomas, 1939. Price, $4.50.

Epidemic Encephalitis. Etiology, Epidemiology, Treatment. Third Report by the Matheson Commission. WILLARD C. RAPPLEYE, Chairman. HAVEN EMERSON, ALPHONSE R. DOCHEZ, FREDERICK P. GAY, WILLIAM H. PARK, CHARLES R. STOCKARD, FREDERICK TILNEY, WILLIS D. WOOD. HUBERT S. HOWE, Secretary. JOSEPHINE B. NEAL, Executive Secretary. HELEN HARRINGTON, Epidemiologist. Pp. 493. New York: Columbia University Press, 1939. Price, $3.00.

The Vasomotor System in Anoxia and Asphyxia. A Study of the Adjustment Reactions of the Mammalian Organs. (Illinois Medical and Dental Monographs, Vol. 2, No. 2.) By ERNST GELLHORN, M.D., PH.D., Professor of Physiology, and EDWARD H. LAMBERT, M.D. Pp. 71; 21 illustrations. Urbana, Ill.: The University of Illinois Press, 1939. Price, $1.00.

Les Infections Humaines a B. Bipolaris Septicus (Pasteurelloses). By ROBERT REGAMEY, Assistant à l'Institut d'Hygiène et de Bactériologie de l'Université de Berne et Chef du laboratoire de recherches expérimentales à l'Institut sérothérapique et vaccinal Suisse à Berne. Pp. 126; 3 illustrations. Berne: Hans Huber, 1939.

John Howard (1726–1790). Hospital and Prison Reformer: A Bibliography. By LEONA BAUMGARTNER, M.D., PH.D. With Introduction by ARNOLD M. MUIRHEAD, M.A. (OXON.). Pp. 79; 9 illustrations. Baltimore: The Johns Hopkins Press, 1939. Price, $1.00.

Medical Climatology. Climatic and Weather Influences in Health and Disease. By CLARENCE A. MILLS, PH.D., M.D., Professor of Experimental Medicine, University of Cincinnati. Pp. 296; 90 illustrations. Springfield, Ill.: Charles C Thomas, 1939. Price, $4.50.

The Harvey Lectures, Series XXXIV. Delivered under the Auspices of The Harvey Society of New York, 1938–1939. Under the Patronage of the New York Academy of Medicine, by DRS. G. F. MARRIAN, A. A. WEECH, E. F. DU BOIS, E. J. COHN, E. A. PARK, K. LINDERSTRØM-LANG, C. H. DANFORTH, A. SZENT-GYÖRGYI. Pp. 279; illustrated. Baltimore: The Williams & Wilkins Company, 1939. Price, $4.00.

Sclerosing Therapy. The Injection Treatment of Hernia, Hydrocele, Varicose Veins and Hemorrhoids. Edited by FRANK C. YEOMANS, M.D., F.A.C.S., M.R.S.M. (LONDON, HON.), Professor of Proctology and Attending Surgeon, New York Polyclinic Medical School and Hospital, etc. Pp. 336; 117 illustrations. Baltimore: The Williams & Wilkins Company, 1939 (A William Wood Book). Price, $6.00.

Functional Disorders of the Foot. Their Diagnosis and Treatment. By FRANK D. DICKSON, M.D., F.A.C.S., Orthopedic Surgeon, St. Luke's, Kansas City General, and Wheatley Hospitals, Kansas City, Mo., Providence Hospital, Kansas City, Kansas, and REX L. DIVELEY, A.B., M.D., F.A.C.S., Orthopedic Surgeon, St. Luke's, Kansas City General, Research, and Wheatley Hospitals, Kansas City, Mo., Providence Hospital, Kansas City, Kansas. Pp. 305; 202 illustrations. Philadelphia: J. B. Lippincott Company, 1939. Price, $5.00.

An Introduction to Modern Genetics. By C. H. WADDINGTON, Sc.D., Fellow of Christ's College, Cambridge. Pp. 441; 159 illustrations, 5 plates. New York: The Macmillan Company, 1939. Price, $4.00.

Nitrous Oxide-oxygen Anesthesia. McKesson-Clement Viewpoint and Technique. By F. W. CLEMENT, M.D., Director of Anesthesia at Flower Hospital, the State Hospital for the Insane, Lucas County Hospital, Toledo Dental Dispensary; Anesthetist to Toledo, Mercy and St. Vincent's Hospitals, Toledo, etc. Pp. 274; 70 illustrations. Philadelphia: Lea & Febiger, 1939. Price, $4.00.

The Rectum and Colon. By E. PARKER HAYDEN, A.B., M.D., F.A.C.S., Assistant in Surgery in the Harvard Medical School, Boston; Assistant Surgeon and Chief of Rectal Clinic, Massachusetts General Hospital, Boston. Pp. 434; 169 illustrations. Philadelphia: Lea & Febiger, 1939. Price, $5.50.

Sterility and Impaired Fertility. Pathogenesis, Diagnosis and Treatment. By CEDRIC LANE-ROBERTS, M.S., F.R.C.S., F.R.C.O.G., Gynæcological Surgeon, Royal Northern Hospital; Consulting Obstetric Surgeon, Queen Charlotte's Hospital, ALBERT SHARMAN, M.D., M.R.C.O.G., Assistant Surgeon, Royal Samaritan Hospital for Women, Glasgow, KENNETH WALKER, F.R.C.S., Surgeon to the Genito-urinary Department, Royal Northern Hospital, and to St. Paul's Hospital, B. P. WIESNER, D.Sc., PH.D., F.R.S.E., Consulting Biologist, Royal Northern Hospital. With a Foreword by the RT. HON. LORD HORDER, G.C.V.O., M.D., F.R.C.P. Pp. 419; 87 illustrations. New York: Paul B. Hoeber, Inc., 1939. Price, $5.50.

Symposium on the Synapse. By HERBERT S. GASSER, JOSEPH ERLANGER, DETLEV W. BRONK, RAFAEL LORENTEDE NO, ALEXANDER FORBES. (Reprinted from *Journal of Neurophysiology*, **2**, 361-472, 1939.) Pp. 113; illustrated. Springfield, Ill.: Charles C Thomas, 1939. Price, Paper, $1.50; Bound, $2.00.

Brucellosis in Man and Animals. By I. FOREST HUDDLESON, D.V.M., M.S., PH.D., Research Professor in Bacteriology, Michigan State College. Contributing Authors: A. V. HARDY, M.S., M.D., DR.P.H., Associate Professor of Epidemiology, De Lamar Institute of Public Health, Columbia University Medical School; Consultant, U. S. Public Health Service, J. E. DEBONO, M.D., M.R.C.P., Professor of Pharmacology and Therapeutics, Royal University of Malta, WARD GILTNER, D.V.M., M.S., DR.P.H., Dean of Veterinary Division and Professor of Bacteriology, Michigan State College. Pp. 339; 40 illustrations (some in color). New York: The Commonwealth Fund, 1939. Price, $3.50.

The Story of Surgery. By HARVEY GRAHAM. With a Foreword by OLIVER ST. JOHN GOGARTY. Pp. 425; 23 plates and frontispiece. New York: Doubleday, Doran & Co., Inc., 1939. Price, $3.75.

The New International Clinics, Vol. III (N.S. II), September, 1939. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia. With 17 Collaborators. Pp. 332; many illustrations, 1 colored plate. Philadelphia: J. B. Lippincott Company, 1939.

NEW EDITIONS.

The Infant and Child in Health and Disease. With Special Reference to Nursing Care. By JOHN ZAHORSKY, A.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine, and Pediatrician-in-Chief to the St. Mary's Group of Hospitals, etc., and ELIZABETH NOYES, R.N., Supervisor and Instructor of Pediatrics, Children's Hospital, San Francisco. Pp. 496; 140 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1939. Price, $3.00.

The Art of Anesthesia. By PALUEL J. FLAGG, M.D., Visiting Anesthetist to Manhattan Eye and Ear Hospital; Consulting Anesthetist to St. Vincent's Hospital, New York, and to Woman's, Sea View, Jamaica, Mt. Vernon, Flushing, Mary Immaculate and St. Mary's Hospitals, Far Rockaway, New York, etc. Pp. 491; 161 illustrations. Sixth edition, revised. Philadelphia: J. B. Lippincott Company, 1939. Price, $6.00.

Surgical Applied Anatomy. By SIR FREDERICK TREVES, BART. Pp. 748; 192 illustrations (66 in color). Tenth edition, revised by LAMBERT ROGERS, M.Sc., F.R.C.S., F.R.C.S.E., F.R.A.C.S., F.A.C.S., Professor of Surgery, University of Wales; Honorary Surgeon and Director of the Surgical Unit, Cardiff Royal Infirmary, etc. Revised from the ninth edition, prepared by the late PROF. C. C. CHOYCE, C.M.G., C.B.E., M.D., F.R.C.S. Philadelphia: Lea & Febiger, 1939. Price, $4.50.

Protozoölogy. By RICHARD ROKSABRO KUDO, D.Sc., Associate Professor of Zoölogy, The University of Illinois. Enlarged and completely rewritten edition of Handbook of Protozoölogy. Pp. 689; 291 illustrations. Second edition. Springfield, Ill.: Charles C Thomas, 1939. Price, $6.50.

Eye, Ear, Nose and Throat Manual for Nurses. By ROY H. PARKINSON, M.D., F.A.C.S., Head Oculist and Aurist to St. Joseph's Hospital, San Francisco. Pp. 243; 79 illustrations. Fourth edition. St. Louis: The C. V. Mosby Company, 1939. Price, $2.25.

Diseases of the Skin. By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (EDIN.), Professor of Dermatology, University of Kansas, School of Medicine, and RICHARD L. SUTTON, JR., A.M., M.D., L.R.C.P. (EDIN.), Associate in Dermatology, University of Kansas, School of Medicine. Pp. 1549; 1452 illustrations and 21 colored plates. Tenth edition, revised, enlarged and reset. St. Louis: The C. V. Mosby Company, 1939. Price, $15.00.

Clinical Diagnosis by Laboratory Methods. By JAMES CAMPBELL TODD, PH.B., M.D., Late Professor of Clinical Pathology, University of Colorado, School of Medicine, and ARTHUR HAWLEY SANFORD, A.M., M.D., Professor of Clinical Pathology, University of Minnesota (The Mayo Foundation); Head of Division on Clinical Laboratories, Mayo Clinic. Pp. 841; 368 illustrations (29 in colors). Ninth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1939. Price, $6.00.

PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS.

UNDER THE CHARGE OF
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PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,
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THE VAGINA.

Artificial Vagina. There has been a definite tendency of late to get away from the Schubert and Baldwin operations in cases in which an artificial vagina must be made. Such operations were reasonably satisfactory, but since they involved resection of the rectum or lower ileum, they were accompanied by a mortality rate, which, although not excessively high, carried too great a risk for an operation which is not a life-saving procedure. It is generally agreed as stated by Dannreuther[5] that surgical interference is justified in a young, attractive girl with secondary sex characteristics and sex urge, particularly if contemplating matrimony and who is so unfortunate as to have been born without a vagina. He has performed and recommends the Frank-Geist operation which includes three distinct operative steps, with interspersed minor procedures, numerous dressings and meticulous attention to detail. The first operation consists of making a skin flap on the inner aspect of the thigh 6½ inches long and 3 inches wide and converting it into a pedicle tube, closing the adjacent edges under the tube. Four weeks later the distal attachment of the pedicle is severed from the thigh and the undersurface of the tube is reopened throughout its entire length. A space is then dissected between the bladder and rectum into which the pedicled flap is inserted after suturing it over a vaginal plug with the skin surface on the inside. The lower edge of the transplant is sutured to the vaginal outlet and the plug is maintained in place by means of a rubber sponge and tight binder. After 3 more weeks the attached end of the flap is divided a little at a time. The patient is discharged from the hospital 2 weeks later although the vaginal plug is worn continuously for several weeks thereafter. A vaginal dilator must be passed every day for a year to prevent contraction and if the patient does not marry, the plug should be worn at night. This operation has also been endorsed by Flynn and Duckett[9] who state that while the operative technique is of great importance, the postoperative management must be rigidly observed, since the chief cause of failure is scar formation and contracture which rapidly

close the lumen of the new canal. Dilatation should be begun early, repeated frequently and prolonged indefinitely.

This type of operation has been modified by Douglass[7] so that it can be performed in one stage and the patient discharged from the hospital in 1 month. He makes four flaps, two from the labia minora and two from the inner surface of the thighs and these are sutured into a prepared vaginal space and held in place by a pack of vaseline gauze. Although he reports only 1 case, the end result was satisfactory and obviously considerable time and trouble was saved.

In the case reported by Glowinski[11] the peritoneum of the pouch of Douglas was used in the construction of an artificial vagina. It is interesting to note that the patient was 33 years old and had been married 3 years before she sought surgical aid. In addition to an absent vagina the uterus was also absent. The operation consisted of a transverse incision at the site where the vagina should have been, followed by blunt dissection upward between the rectum and bladder until the peritoneum was reached. A large Hegar dilator was placed well up in this canal and held there tightly. The abdomen was then opened through a transverse incision just above the symphysis and the place where the Hegar dilator was pushing against the peritoneum of the pelvis was exposed. The peritoneum at this site was incised, mobilized and by means of long catgut sutures was drawn down into the previously prepared vaginal canal and sutured to the structures at the vagina outlet which had also been previously mobilized. A large tampon was placed in this new canal from the abdominal opening and the peritoneum was closed over it, thus forming a small peritoneal sac separate from the general abdominal cavity. The abdomen was then closed in the usual manner. The tampon was allowed to remain for 4 days after which saline douches were given. The vagina thus made admitted two fingers, was about 8 cm. long and it became covered with smooth epithelium. After 4 years of observation the vagina had not decreased in size and was perfectly satisfactory from the functional standpoint. The operation has a slight risk and can be used in any case where the uterus is also absent.

Based upon 32 cases reported, including 2 of his own, Barrows[2] believes that the Kirschner-Wagner operation has the advantages of no risk to life, simplicity of technique, no bad scars and short period of hospitalization. The operation consists of preparing a vaginal canal as in the other operations and inserting a rubber sponge prosthesis covered with Thiersch grafts with the skin surface inside. The resiliency of the rubber sponge keeps the grafts in contact with the raw walls of the canal for 8 or 10 days, at which time most of the grafts have taken. Postoperative dilatation is imperative.

Counseller[4] has modified this operation by using a flexible rubber tube over which the graft is placed. The tube can be cut to any desired length, which is necessary because the length of the canal is variable, and is removed in from 10 to 14 days and replaced by a bakelite sound which is made especially for each patient. The sound is held in place by a sanitary belt and is worn for 6 months, being removed once daily for cleaning. He states that the management of vaginal stricture is

more difficult than that of congenital absence of the vagina. Extreme care must be used to avoid injury to the urethra, bladder and rectum, since it is necessary to form the new vaginal tract by sharp dissection through dense and often inflamed scar tissue. The cervix should be located if possible, so that the patient can again menstruate. When the cervix can be located, it is pulled into the rubber tube over which the graft is placed. The grafts then grow over the anterior and posterior vaults leaving the cervix exposed.

A simple method of constructing a vagina has been described by Wharton[27] based upon the principle that the vaginal epithelium has remarkable powers of proliferation and in a relatively short time will cover a raw surface. Another new feature is the use of a plug or mold to keep the new vaginal cavity open, this mold being composed of a rubber condom filled with some fairly firm substance such as paraffin or balsa wood. The operation consists of dissecting a space between the bladder and rectum and then introducing the vaginal mold, the whole operation taking only 10 or 15 minutes. The mold is allowed to remain in the vagina for 3 weeks, during which time it requires no attention except to be sure that it does not come out. The patient is kept in bed as long as the condom is in place. There are two important details to observe in preparing the vaginal canal. First, the space must be larger than one expects it to be eventually, to allow for contraction during convalescence due to the slipping of the mold or pressure from surrounding organs. The second point of importance is to have good hemostasis, paying especial attention to the vaginal branches of the uterine arteries, which are at the level of the broad ligament on each side. The condom mold should be flush with the vestibule after it has been inserted and the perineum must be inspected several times daily to see that it remains in place and is causing no edema or pressure changes. The patient is advised to change her position in bed frequently so that the weight of the vaginal form will be evenly distributed. After leaving the hospital coitus is prohibited until 2 or 3 months have passed or until the vaginal epithelium has become thick and tough. During this time a loose vaginal plug is worn at night. If the first operation does not provide a vagina of satisfactory size it can easily be enlarged subsequently. Since the vaginal space is lined by epithelium which proliferates from the vestibule or the rudimentary vagina, this operation is feasible only when there is some vaginal epithelium to start with and he hesitates to recommend it when there is complete absence of all mucous membrane. He has performed the operation in 4 cases, in 2 of whom follow-up results have been satisfactory.

As simple as this operation seems, the method suggested by Frank[10] is even simpler, since no operation involving incision is done. He has been struck by the very thin tissues which separate the rectum from the bladder in these cases and he has attempted to force inward the mucous membrane in the introital region without incision and has found that a vagina may be readily established. The first object is to establish a narrow canal at least $2\frac{1}{2}$ inches long as quickly as possible. After this depth has been attained, enlargement of the canal follows. The

first step is important. A narrow pyrex tube, 0.8 cm. outside diameter, is introduced by the physician in the hymeneal region in a direction backward and inward with the patient in the lithotomy position. The patient is carefully taught to perform this maneuver 3 times daily for at least ½ hour for 1 week. This is important in order to stretch the mucosa so that further measures do not distort and dilate the urinary meatus. After the first week, the patient inserts the tube as before and then changes the direction of insertion in a line paralleling the normal axis of the vagina. The tube is held in place for ½ hour morning and evening. Usually in from 2 to 4 weeks a sufficient depression permitting the retention of a 3-inch-long tube has been attained. This is kept in place at night by a binder. The patients are warned not to apply excessive force as evidenced by bloody spotting. The diameter of the tube is gradually increased until a 2 cm. size is reached and this is kept in the vagina every night for from 8 to 10 hours until marriage. He reports the use of this method in 6 patients in only 1 of whom was there a failure.

Gonorrheal Vaginitis. An unusual amount of attention has been paid to the subject of gonorrheal vaginitis in recent years and a review of this kind can do no more than attempt to present the conclusions reached by some of the leaders in this field. From the evidence obtained in a large series of cases in which smears and cultures were made, Ruys[22] of Amsterdam believes that gonorrheal vaginitis occurs only in the acute form and is always complicated by gonorrhea of the rectum. It is recognized that in many cases of vaginitis there is no history of an acute attack. The children suffer from a chronic state of irritation with a varying degree of secretion. They often look pale and have a severe local inflammation, but in these cases the smears and cultures show different bacilli and cocci in varying quantities and it is difficult to conclude whether these bacteria are of etiologic importance or are merely secondary invaders. The success of hospital treatment in such children, Ruys believes, is due more to the improvement of the general health conditions than to local treatment. It should be remembered that foreign bodies and parasites in the vagina can give rise to severe local symptoms. In the series reported which were very carefully studied, only 57 of the 292 children with vaginitis actually had gonorrhea.

There has been great interest in the estrin treatment of this condition since Lewis[17] presented it 6 years ago and there has been considerable speculation as to how it works. Lewis and Weinstein[19] have found that the administration of estrin to children renders the vaginal secretions strongly acid and they believe that this acidity in all likelihood is the important factor. Lewis and Adler[18] state that in normal children the reaction of the vaginal secretions is nearly neutral (usually between pH 6.8 and 8.4) and when the vaginal mucosa reacts to estrogenic substances the secretions become markedly acid (pH 4.8 to 6). *In vitro* the gonococcus grows best in a faintly alkaline medium (pH 7.2 to 7.6). If this is rendered acid very gradually over a period of days or weeks these organisms will rarely adapt themselves to a medium as acid as pH 6 to 6.2. The production of acidity in the vagina is good evidence

of the effectiveness of estrin, it is easily determined and is much simpler than the taking of biopsies for the determination of epithelial cornification as was done in the early work.

The cure of 175 patients with gonorrheal vaginitis by the use of estrin is reported by Te Linde.[26] Except for 16 who received the product hypodermically in oil, all were treated by the use of vaginal suppositories. He has failed to encounter a patient who did not get well by this method of treatment and naturally he considers it a very satisfactory method of handling these little patients. A follow-up examination of the first 100 patients, from 3 months to $2\frac{1}{2}$ years after the last treatment, showed 98 of them well. There has been no clinical evidence of harm due to the treatment. He agrees in part with Lewis that the increased acidity brought about in the vagina by the action of the estrin is a factor in overcoming the infection, but since his results were not nearly so good when another acidifying suppository was used, he feels that there must be some other factor involved as well, probably the increased thickness of the vaginal epithelium which prevents reinfection of the subepithelial tissues and thus permits the inflammatory process in them to subside. He has found that by giving a suppository containing 600 international units daily, the vaginal epithelial response is noted in 13 days and the smears become permanently negative in 18 days. Treatment is usually continued for several days afterward so that the average total time of treatment is slightly less than 27 days. This is surely a different story from the days when we treated these patients for months or years, often without permanent relief.

In the opinion of Mazer and Shechter[20] the good effect of estrogenic substances in this disease lies in its ability to create a temporary maturity of the vagina and thus render it resistant to pathogenic bacteria, but they emphasize that the pH of the vaginal secretions must be reduced below 6. To safeguard against recurrence of the infection, treatment should be continued for 8 weeks even though there is earlier clinical and bacteriologic cure. In their series, hypodermic injections cured 78 of 81 children with a 10% incidence of recurrence; vaginal suppositories cured 33 of 34 children without any recurrence in the 26 children who were observed for a long time; oral treatment was ineffective in 3 children who received as much as 1500 rat units daily for a period of 8 weeks. Side effects, such as pubic hair, uterine bleeding and enlargement of the breasts, are temporary and are more frequently encountered with hypodermic than with local treatment.

Since sulphanilamide was found to be of value in gonorrhea soon after it was presented to the profession, it is quite natural that it should have been tried in the treatment of vaginitis due to this organism. In reporting their experiences with this drug at the Cook County Hospital in Chicago, Hoffman, Schneider, Blatt and Herrold[15] have not obtained outstanding results. In a series of 25 patients who were given sulphanilamide, 7 were cured in an average of 17.3 days and 9 more in an average of 42.9 days. Only 2 of the 9 remaining patients were cured by additional administration of the drug. A standard dose was used in all and the results suggest the futility of the continuation

of more than two standard courses of treatment. The children tolerated the drug extremely well as compared to adults.

Schauffler, Kanzler and Schauffler[23] have collected 261 cases of vaginitis treated by sulphanilamide in 18 teaching institutions and by 10 individual observers and have come to the conclusion that hospitalization is necessary in giving this type of treatment. Continuous medication, rest, blood studies and careful observation will remain essential until the limits of safety can be more clearly delineated. Since from all other angles hospitalization in this contagious disease is definitely contraindicated, this must be considered a disadvantage. Of the collected opinions in this study, the total consensus was only 55% favorable for the drug, it being regarded as inferior to other methods of treatment by the majority and nearly one-half will discontinue its use in this connection. Low dosage and failure to maintain the blood concentration may be responsible for some of the poor results, but the possibility of a connection between the desired acid reaction of the vagina and the unfavorable effect of an acid reaction on the action of sulphanilamide should be considered.

For purposes of comparison, the series of 112 cases reported by Burpee, Robinow and Leslie[3] is of interest, as several methods of treatment were employed. The intramuscular injection of estrin in oil gave 41 cures in 47 cases, but in 5 of these there were later recurrences. Five patients treated by a combination of estrin and 1% silver nitrate jelly locally were cured with no recurrences. Nineteen cases received fever therapy alone, produced either by injection of typhoid vaccine or by the Kettering hypertherm, with 8 cures and no recurrences. Twenty-two patients received sulphanilamide alone and of these 11 were cured and there was 1 recurrence, all of the cures being obtained in less than 2 weeks. Increase of the dose, prolongation of the treatment and combination with fever therapy did not improve the results.

Trichomonas Vaginalis Vaginitis. In an article which evaluates the various types of treatment of vaginitis associated with *Trichomonas vaginalis*, Hesseltine[13] states that at the present time the drastic scrubbing procedures of a few years ago have almost been replaced by a dry technique, with the patient self-administering much of the treatment. He compared the effect obtained by the use of 3 arsenical preparations, 1 silver picrate and 2 lactose combinations, the control patients receiving the preparation minus the supposed active ingredient. In order to be considered cured, the patient had to go through two consecutive menstrual periods without treatment, remain free from symptoms and present no clinical or laboratory evidence of the disease. He found that good results may be obtained with various agents in approximately 85 to 90% of the patients, while the remaining 10 to 15% may not remain relieved or may even fail to be improved. Probably in from 8 to 15% of the cases particular care should be taken to eliminate foci of infection from the patient's rectum, urethra or bladder, or from the husband's urethra or prostate.

Since protozoa in general are sensitive to variations in osmotic pressure of the surrounding medium, it occurred to Rosenthal, Schwartz and Kaldor[21] that this vaginal protozoön may also be affected by such

variations and they decided to study the action on it of hypertonic salt solution. They experimented with four dilutions of sodium chloride, namely 3, 6, 12 and 25%. The 3 and 6% salt solutions apparently did not affect the parasite, but entirely different pictures were obtained when salt solutions of 12 and 25% were used. The motility of the parasites stopped instantaneously and their shape underwent a radical change. The parasites became shrunken and crenated and to all appearances were dead. When the parasites were transferred immediately after their inactivation from a 12% solution into a physiologic solution their normal shape and motility were restored. The 25% salt solution, however, made the inactivation permanent and irreversible. On the basis of these laboratory findings they treated over 50 cases with a 25% salt solution douche and in nearly all cases the relief was prompt after 1 or 2 daily douches. The itch disappeared, the discharge became scanty, thin in character and odorless, or even disappeared entirely, and the vaginal mucosa assumed a normal appearance. In 30 cases, no more organisms could be found after 2 or 3 douches. Twenty-four cases showed complete absence of live parasites after 1 week of daily douches and 2 cases required 2 weeks of daily douches to bring about the disappearance of the parasites.

In order to determine the incidence of *Trichomonas vaginalis* and its pathogenicity, Jacoby and Der Brucke[16] examined 300 consecutive patients for the organism and found them in 50 (16.6%). Of the patients in whom the organism was found, 16% had no discharge of any kind and 24% had only a slight discharge. Only a third of the patients complained of itching or had any evidence of vaginitis. They believe that the trichomonas is essentially a surface parasite and can readily be washed away by a simple douche and that it is a non-pathogenic invader of the normal or diseased vaginal tract. If it invades a normal vagina, no symptoms are produced, while in the diseased vagina the symptoms are those of the disease present and are not initiated by the trichomonas. Treatment for its destruction is not necessary in their opinion, but effective treatment of the underlying inflammatory condition, cervical or vaginal, will cure the patient. The treatment that yielded the best results in their hands was that directed toward the elimination of the chronic congestive condition in the pelvis and not paying any attention to the trichomonas itself. With the eradication of the causative factor in the pelvis and eliminating stasis, all of the symptoms disappeared in 75% and the organisms disappeared in 91.6% of their cases.

It has long been known that trichomonads are found in other locations than in the vagina. Among 58 women examined by Stein and Cope,[25] all of them having *Trichomonas vaginalis* vaginitis, trichomonads were found in the gums in 3, in the stools in 3, and in the catheterized urine in 5. It is apparent from this observation that there is no causal relationship between the vaginal incidence and that of other common sites of trichomonads in the body. Moreover, there are cultural characteristics which differentiate the vaginal trichomonas from the buccal and intestinal types. While occasional instances of infection of husband and wife, and 1 case of infection of 3 female members of the same family

are reported, the evidence is insufficient to conclude that it is directly transmitted from person to person. The source of the trichomonads in the vagina is unknown and it is unlikely that they may migrate from the other common sites in the body. In spite of other reports, they still believe that *Trichomonas vaginalis* is pathogenic, that it is a specific species and that it is apparently in symbiosis with the bacteria commonly found in the vagina.

Hibbert and Falls[14] present evidence which they believe demonstrates that the *Streptococcus subacidus* is the causative factor in this type of vaginitis. They recall that *Trichomonas vaginalis* may be present for long periods of time in the vaginal secretion without producing symptoms, and conversely, there are many cases having all the symptoms of trichomonas vaginitis which fail repeatedly to reveal the presence of the parasite in the discharge. Having isolated the *Streptococcus subacidus* from the discharge of their patients, they inoculated 5 other patients with a pure culture of the organism, in 4 of which definite vaginitis was produced as evidenced by intense redness of the cervix, vaginal mucosa and vulva and a gray-white sticky discharge and the patients all complained of tenderness, burning and itching. These patients were then treated by means of the application of a broth filtrate of the *Streptococcus subacidus* to the cervix and vagina, together with intracutaneous injection of a vaccine made from this organism. The treatments were given once a week and all were cured in from 4 to 7 treatments. From all of the foregoing opinions it may be gathered that while there is not unanimity as to the importance of the protozoön, the tendency is to treat the associated vaginitis with much milder methods than formerly or even to ignore it as such and treat the general condition of the patient.

Senile Vaginitis. After an artificial or natural menopause there are physiologic atrophic changes which occur in the genital organs which consist of a shortening and constriction of the vagina, particularly at the introitus, together with a loss of elasticity and distensibility of the vaginal walls. Davis[6] states that senile vaginitis follows an inflammation superimposed on the atrophic mucosa of the vagina. The exciting factor may be an irritating uterine discharge which macerates the atrophic vaginal epithelium or a recurring minor trauma which injures it. The usual pathogenic organisms in the vagina invade these denuded unprotected areas and start an inflammation, causing superficial ulcerations or erosions which appear as small punctate hemorrhagic areas. Sometimes the denuded areas become fused together and form adhesions which, in severe cases, may hide the cervix or even close the vaginal lumen. The symptoms of this type of vaginitis are discharge and burning, pelvic pain, burning on urination and pruritus. Assuming that the changes in senile vaginitis would disappear if the mucosa could be restored to the type present during active sex life, Davis thought it worth while to try the effect of estrogenic hormones in such cases. He treated his patients with 100 rat units of estrogenic hormone subcutaneously 3 times weekly and in addition a suppository containing 75 rat units was inserted into the vagina every night. The average patient was treated for 6 weeks, although in most instances

the symptoms disappeared after 10 days. The changes in the vaginal mucosa as the result of this treatment were most interesting. The inactive basal cells began to proliferate, the cells soon contained an abundance of glycogen and the inflammatory foci beneath the squamous epithelium disappeared. These changes, however, were not permanent. Several weeks after the cessation of treatment the mucosa rapidly returned to its previous condition of atrophy but the patient's symptoms did not return unless she had not received enough treatment and some inflammation still remained. If trauma and infection are again introduced, senile vaginitis will undoubtedly recur.

Inquiring into the dietary habits of 50 patients with senile vaginitis, Simpson and Mason[24] found that the majority existed largely upon a diet consisting of toast and coffee for breakfast, thin soup and side meat, corn bread and jam for lunch, some form of pork and one or two vegetables for supper. Sweets and desserts were prominent in all the diets. In many instances distinct lack of desire for butter, eggs, fresh meat and milk was noted. Such diets, obviously low in vitamin A, are peculiar to elderly women. In some patients, chronic digestive disturbances and habitual use of mineral oil were also suggestive of impaired absorption and utilization of vitamin A from the diet. For this reason they treated their patients by the administration of cod- or halibut-liver oil 3 times daily with or without the use of plain tap water douches. The treatment proved unusually effective in producing rapid relief of symptoms and in the gross and histologic repair of the vaginal mucosa.

A different method of approach in the treatment of this disease has been taken by Adair and Hesseltine,[1] who believe that in bacterial infections the epithelial cells and their glycogen-like content need stimulation as well as the protection of an increased vaginal acidity. For this purpose they used a mixture of lactose (95%) and citric acid (5%) which the patient inserts into the vagina each night. This mixture favors the growth of the normal vaginal bacilli and senile vaginitis cases have been cured by this method in an average of 4.5 months. From the above diverse methods of treatment it may be observed that the basic principles of all of them depend upon improving the nutrition of the vagina and the avoidance of trauma and reinfection.

Vaginal Hernia. In presenting a case of vaginal hernia, Hall[12] has reviewed the literature of this rare condition and has assembled some interesting facts. In this type of hernia the peritoneum is pushed downward through the pelvic floor into the vaginal vault or along the wall between the vagina and the rectum or bladder, sometimes extending between them all the way to the perineum and it is of interest in the differential diagnosis of cystocele and rectocele and as a complication of uterine prolapse. These hernias all have a separate peritoneal sac, which cystocele and rectocele do not have, and a definite ring which is absent in uterine prolapse. Most masses in the upper part of the vagina are first considered rectoceles. However, one should note that the hernia appears when the patient stands, coughs or strains, disappears when she is in a recumbent position, has a definite hernial ring, gurgles on manual replacement of the bowel and has no connection with the rectum, although it may be accompanied by a rectocele.

Usually the hernia merely causes some discomfort but in 25% of the cases there are complications and in one-third of these there is a fatal termination. If the condition develops during labor, the signs may be those of shock and intestinal obstruction. The treatment in such a case is immediate return of the head and reduction of the hernia. Obstruction and strangulation from other causes demand immediate surgery. Operation may be done by the abdominal, perineal or combined approach and the insertion of ureteral catheters before operation is advised.

Cancer of Vagina. A study based upon 37 cases of primary cancer of the vagina has been presented by Emmert,[8] the youngest patient being 26, the oldest 82 (average age, 53 years). Previous labors seem to have little to do with the etiology, since 7 of the patients were nulliparous; and if parity had any influence, primary cancer should be much more common, its incidence in this study being only about 1% of genital cancer. Of the 37 patients, 4 were treated purely palliatively with acetone, because their condition was too far advanced for any hope of cure. Radium treatment was given to 21 patients of whom 19 were followed. Four of these are alive 11, 8, 7 and 1 years, respectively, after treatment. Five patients were subjected to radical colpectomy and vaginal hysterectomy. There was 1 postoperative death and 2 of the others are alive $6\frac{1}{2}$ and $1\frac{1}{2}$ years later; a third case is alive with recurrence. From his study he admits that the hopes based on operation and radium therapy in this disease have not yet been fulfilled since the curability rate is but 12%. He advises that in the early stages of the disease a really radical operation should be performed, while radium with or without Roentgen rays should be applied in the more advanced cases.

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DERMATOLOGY AND SYPHILOLOGY.

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THE PSYCHONEUROGENOUS COMPONENT OF CUTANEOUS REACTION MECHANISMS.

As Foster Kennedy[59a] remarked in discussing the emotional background of the skin, "If one were to speak of and stand by only those things which one knows, there would be a great silence in the world." He concedes, however, that deliberations on the subject keep the mind active, even if they do not always cure the disease. The notable increase in significant work in the field of psychosomatic relations extends to the skin no less than and perhaps more than to other structures. In naming some of the important workers and summaries, a gesture of admiration and respect must go to H. Flanders Dunbar,[32] for her monumental summarization of the entire literature of the psychosomatic field in which the cutaneous division occupies 38 of 432 pages of text, with 120 bibliographic titles.

The father of cutaneous neuropsychiatry, so to speak, is W. Theodore Sack[86] whose summarization of the subject appears in the Jadassohn Handbuch. The Barber-Gillespie[5,38] group at Guy's Hospital, including Drake,[30a,b] Rogerson,[81,82] and Strauss,[99] constitutes probably the most important group now active in the field. In this country Klauder[60a–d] and Hazen[48] have initiated and kept alive much of the American interest in the subject. Becker[8a,b,76,101] and his co-workers have concerned themselves with functional dermatology from the neurovascular standpoint. Many highly significant investigations have come by way of fundamental vascular and neural physiology, as in the Lewis-Dale[24,25,67] conception applied to the skin. Psychoneurogenous considerations have been hobby interests of various clinics such as that of Bloch[12] (Zurich) and the University of Pennsylvania.[9,92a–f,93,95–98] The extended British and German work on asthma has established important correlations in the cutaneous field. Psychotherapy and hypnosis, the latter especially, have been studied by Kartamischew,[56a–e] Wisch[106] and Bunnemann.[18] It is impossible to overestimate the importance of the contributions of workers in what at first glance seems to be unrelated fields, such as that of gastro-intestinal physiology and cutaneous mycology and bacteriology. In general, allergists interested

in dermatology have seen few neuropsychiatric bearings (Walzer[103]) with the exception of Duke[31a] (emotional urticaria).

Fundamental Physiologic-neurologic Linkage and Basic Mechanism —Vascular and Vasculo-visceral Fields.—Skin color as an expression of vasomotor and hence frequently emotional reactivity has had vigorous emphasis at the hands of all clinical observers. There has, however, been a notable deficiency of colorimetric studies of the influence of emotion on the vasomotor mechanism. One reason for this has been the slowness and cumbersomeness of spectrophotometry as demonstrated by the apparatus of Sheard[45] and others. It is possible that the improvement effected by Hardy[44] may make possible direct analysis of the emotional color changes, through the psychogalvanic reflex which has been thought to reflect the state of the terminal capillaries in the skin (Densham and Wells,[27a,b] contradicted by Darrow[26]). The notable possibilities of skin temperature study, which is a reflection of blood supply and vasomotor tone, are admirably illustrated by Mittelmann and Wolff[74] who, with special apparatus under controlled temperature and other conditions, investigated the relations of mood, of the presence of observers, and of the repeated discussion of life situations in a subject with growing tension and despair. The discussion of impersonal topics; awareness and insight; moderate and intense emotional stress in normal subjects and in one with Graves' disease; the major temperature changes in the Raynaud syndrome; and the effects of sympathectomy were objectively studied. Ziegler and Cash[107] review a considerable literature. Their material was largely psychopathic; a wide variability of reaction was observed; the opinion was expressed that cerebral heat control is centered in the hypothalamus. Bazett's[7] work on skin temperature is mainly on cerebral localization of heat centers (cats).

The Sweat Mechanism. The influence of sweat on the pH of the skin, on the concentration of secreted reducing bodies on the skin surface, and also in the case of certain glands (apocrine) of soluble proteins and odoriferous substances, is one of the important linkage mechanisms in the effect of emotion on pathologic conditions of the skin. Kuno's[64] excellent review of the physiology of human perspiration (1934) gives great weight to the emotional factor in sweating. The two embryologic groups of sweat glands, the apocrine and the eccrine, are clearly differentiated in their behavior by all students of the subject, and an excellent review of what is known of the physiology of the apocrine glands since Schiefferdecker's[87] fundamental investigation is given by Way and Memmesheimer.[104] The eccrine gland secretion is of a markedly lower pH than the apocrine, and it is the secretion of these glands over the largest part of the body surface which maintains quite largely the so-called acid defence mantle. The secretion of the apocrine sweat glands at a much higher pH is much more favorable to the growth of fungi and other infective organisms, and is an important factor in the localization and characteristics of certain dermatoses. Apocrine sweat gland distribution occurs only in the hairy regions of the axillæ, the mons veneris, the perineal and circumanal regions and the anterior abdominal wall and the aureola and hair follicles about the nipple.

Kuno[64] points out in summarizing a number of investigations that the weight of present-day effort tends to show that all sweating is centrally controlled through sympathetic fibers. Pituitrin injected in the region of the hypothalamus *via* the cerebral ventricles gives rise to extraordinary sweating which does not occur when the drug is introduced in other ways (Cushing[23]). The rôle of pituitrin in the production of sweating is, however, by no means clear. The sweat secretion most obviously influenced by mental states is that of the palms, soles and axillæ. Kuno[64] considers this to be controlled by a special center in the midbrain, different from the general sweat control. Inhibition of sweating, like excitation of it, can occur under mental stress.

The interest attaching to the apocrine group of sweat glands arises particularly from their embryogenesis and close relation to the sexual mechanism. They develop at puberty, remain active throughout the larger part of the individual's life, and are markedly influenced by stimulation of the sexual, mental and nervous reactions. So marked is the relation of the apocrine glands to cyclical sexual phenomena in women that they have come to be regarded essentially as accessory sexual glands (Way and Memmesheimer[104]). Loeschcke[68] noticed their participation in the sexual cycle; Waelsch,[102] Kayser[57] and Seitz[89] confirmed these observations, and the studies of Herzenberg[49] have led to the belief that apocrine glands are influenced by physiologic rather than pathologic sexual occurrences. Occasional case reports, and in all probability much unreported material attest the great psychogenetic importance of abnormalities of apocrine sweat secretion. Gillespie,[38] for example, cites the case of a woman whose hyperhidrosis began with her engagement to marry a man whom she did not love, and continued because of the conflict between her sense of duty and her enforced dependence on her husband, with her desire to dissolve the marriage.

The observer has no difficulty parenthetically speaking, in observing the connection between vulvar sweating, sweating about the umbilicus, and sweating in the axilla in women, and various sexual states and episodes, including deprivation of sexual relations, serious grades of conflict involving the fidelity of the husband, and so forth. Unfortunately, most of this material has not as yet been subjected to critical analysis by quantitative test of the amount of sweat secretion in known areas under varying circumstances, and so forth.

Sweating of the palms and soles is well recognized as a close associate of mental effort of many kinds, including even so simple a matter as the addition of a column of figures. That it can be closely associated with psychogenous states is apparent in those patients whose palms never sweat except under special circumstances such as taking leave of a stranger, taking a special form of examination written or oral, and so on. The reported material in this field is small and far less than the importance and experimental possibilities of the work would make possible. A recent technical contribution to the experimental approach has been made by Buley[17] whose apparatus permits the collection of sweat from individual glands and quite accurate estimates of the rate of secretion under various stimuli.

The Gastro-intestinal Mechanism. Stokes and Pillsbury[96] attempted to erect a theory of gastro-intestinal mechanism in emotional and nervous manifestations on the skin based largely upon the work of Spiethoff,[90] Ehrmann,[34] Ryle and Barber,[85] Brown[16] and Eastwood,[33] Knowles and Decker,[61] Rulison,[84] Ayres[4] and others, from the dermatologic side, and Alvarez,[2] Carlson,[21] Hornborg[52] and Bogen,[13] Schrottenbach,[88] Cannon[20] and several observers working with hypnosis, including Bennett and Venables[10] and Heyer.[50] In addition to the contributions dealing largely with gastric hypoacidity under emotional stress, they invoked the effect of gastric secretion on the duodenal bacteriologic flora (Ricen, Sears and Downing[80]), relations between gastric acidity and blood uric acid (whose increase in certain conditions has been credited with etiologic importance), pointed out by Kurti and György;[65] effects on biliary stasis (Ivy,[55] Elman and McMaster[35]); on carbohydrate metabolism (Freud and Saadi-Nazin[37]); on pancreatic secretion (Oechsler[77]); on peristaltic gradients and absorption (Burnett[19], Alvarez and Freedlander[3]); on absorption of histamine-like substances (Kendall and Schmitt[58]); avitaminosis (Koessler, Maurer and Loughlin[62]) as factors of possible importance in the emotional linkage of gastro-intestinal behavior with the reactions of the skin. In addition, these authors call attention to the carbohydrate ingestion factor in gas bacillus proliferation, the work of numerous observers, including Irving and Ferguson[54] and Abrahamson and Miller[1] on the relation of intestinal pH to calcium absorption from the intestinal tract.

Observers of large experience such as Stockton[91] and Alvarez[2] have repeatedly emphasized the importance of psychotherapy in diseases of the intestinal tract, and there is very little doubt that through the psychotherapeutic approach to the gastro-intestinal tract, much can be done with some of its abnormal contributions to the behavior of the skin. Weiss and Collins,[105] in an interesting study of vagotonia and sympathicotonia in relation to the gastro-intestinal tract, reiterate what has been recognized in the skin since Brill,[15] that vagotonia and sympathicotonia can rarely be demonstrated as pure cases of one or the other. They provide a tabular account of the symptomatic accompaniments of vagotonia and of sympathecotonia that should be helpful to the dermatologist called upon to deal with cutaneous conditions in which one or the other of these neurogenous groups of constitutional symptoms appear. Desaux and Antoine,[28] in a suggestive study entitled "Reactions of the Skin to Nerve Reflexes Originating in the Stomach and Intestines in the Adult," lay particular stress on the ability of local pain arising from various causes to give rise to the disturbances of blood flow which probably influence pruritus, and serve as the origin of scratching and of neurodermatitis. They maintain that dilatation of the stomach is capable of producing marked responses both in the sweating and the sebaceous secretory mechanisms of the face. They concede the great importance of the well-known vasodilator effects produced by the gastro-intestinal tract, particularly in the flush area of the face, but recognize no clearly understood mechanism. Menninger,[72] in an interesting discussion of functional disorders of the gastro-intestinal tract, correlates gastro-intestinal symptomatology and function with the personality characteristics of the individual in a way

highly interesting and suggestive to students of the eczema-asthma-hay fever complex with its attendant personality characteristics. The aggressiveness, independence, and ambition of certain gastro-intestinal neurotic types which he regards as overcompensation for a repressed desire to be dependent, to be loved and to be fed, fits in singularly well with the psychologic characteristics of a large group of eczema-asthma-hay fever patients, as described by Rogerson,[81,82] Strauss[99] and others. In Menninger's[72] studies of colitis it is more difficult to find appropriate reflexes on the cutaneous behavior and his views on constipation will probably be better appreciated by psychiatrists than dermatologists. His point, however, is well taken, that all individuals presenting the gastro-intestinal symptomatology frequently accompanying the eczema-asthma-hay fever complex and the various phases of neurodermitis, should have the benefit of an accurate, penetrating and detailed analysis of the psychologic component. "The treatment in all cases must be directed towards the total personality, and not merely towards the stomach or the intestines or the colon" (or the skin). Foster Kennedy,[59b] in a discussion of the nervous relationships of the gastro-intestinal tract, rates this group of structures as the primary ego. He points out the ulcer tendencies of the parasympatheticotonic (vagotonic) individual under repressed emotion, anxiety and heavy responsibility without any direct reference, however, to possible skin correlations. His remark on the allergic relations of emotion—"Recently I was able to show that many allergic persons express their allergic reactions only when their sympathetic symptoms are, as it were, 'triggered' and made more sensitive by emotion," has undoubted dermatologic correlation and explains perhaps why in the eczema-asthma-hay fever complex the large number of allergic reactions, to foods especially, is so fluctuant and variable, and so frequently without significance for the patient's general or cutaneous condition.

Direct Neural and Neurovascular Mechanism. The Lewis-Dale Concept. The extremely important advances included in the work of Sir Thomas Lewis[67] on the "triple reaction" in its relation to herpetic, dermatitic, diffusely inflammatory and urticarial lesions in the skin has been welded with the work of Dale[25] and his associates on the function of acetylcholine as the chemical intermediary between the nerve terminus and the muscle fiber in the parasympathetic factor in the nervous control of circulation and other functions. Several notable papers based on these conceptions dealing particularly with urticaria as a "cholinergic" phenomenon deserve mention. Grant, Pearson and Comeau[41] report observations on urticaria provoked by emotion, exercise and heat in which the clinical correlation described some time before by Duke[31b] is adequately substantiated and the mechanism made clear. These observers found that the urticaria was provoked through efferent peripheral nerves when these were stimulated by emotion, by exercise or by warming the body.

The experimental technique involved the immersion of the legs of a patient with "heat urticaria" in hot water, after the circulation in one arm was obstructed. This was followed by a general urticaria except on the ischemic arm. If warming was stopped, the patient cooled, and the circulation restored; when the rash was subsiding an intense urti-

caria quickly developed on the previously ischemic arm. This indicated clearly that H-substance was released in the skin of the arm while its circulation was arrested, and in response to warming the legs. Grant and his associates adduced "further evidence of the release of H-substance during occlusion" by first congesting the arm before arresting its circulation and repeating the experiment just described. When the urticaria began to develop on the free arm, numerous bluish spots of local vasodilatation appeared in the skin of the congested and occluded arm. These spots were found to mark the places where the wheals quickly appeared when the circulation was restored. The authors believed that this indicated that the stimulus (H-substance) was released in the skin through the peripheral nerves, since the nerve constituted the only functional connection between the ischemic skin where H-substance is released and the body where the stimulus was applied. Blocking of the cutaneous nerves in 3 of the cases prevented the development of the urticaria in the area of distribution of the nerves in response to warming of the legs. They felt that this demonstration was satisfactory to indicate a neurogenic cause for the urticaria. The nerves involved were probably cholinergic since the urticaria was also provoked by choline derivatives given subcutaneously or applied locally. Accordingly, they felt that the urticaria appearing in response to warming the legs was "due to the release of acetylcholine in the skin as a result of the stimulation of cholinergic nerve fibers. This release of acetylcholine in turn leads to the liberation of H-substance from skin cells." Marchionini and Ottenstein[70] had previously suggested that sensitivity of the patient's skin to sweat was an important factor in the production of the urticaria, but Grant and his associates[41] could find no evidence to support this idea. They further described a condition of unresponsiveness of the vessels. Hopkins, Kesten and Hazel,[51] reporting on the clinically familiar emotionally induced urticaria, brought on by anger, were able to confirm the work of Grant and his associates[41] and to extend the observations on urticaria produced by iontophoresis of mecholyl and intradermal injection of various choline derivatives. They confirm the significance of Duke's[31c] classification of these patients into local and general reactors, and they state that the locally produced urticarias have no emotional foundation. In certain subjects (Harris, Lewis and Vaughan[46]) passive transfer of these localized urticaria manifestations indicated that they were circulatory in origin, rather than neurogenous.

Metabolic Studies. There have been practically no notable contributions to this field in some time. Dunbar's[32] review (38 pages) of the subject and its psychogenous relations contains practically no references to skin correlation. The skin reactiveness of hyperthyroid individuals is apparently vascular; that of hypothyroid individuals has not been adequately investigated. The now well-recognized pronounced effect of emotion on sugar metabolism should have its cutaneous correlates, which, however, have had no investigative attention so far as we can ascertain. It would be extremely interesting to determine whether threshold diabetes and lowered sugar tolerance of older patients with long-standing dermatitis and skin infection have any relation to emotional and depressive states. Hypoglycemia has as yet

no etiologic place in cutaneous disease, yet it has very interesting emotional and conduct correlations.

Glaser,[39] confirmed by Kretschmer and Krüger,[63] demonstrated the possibility of influencing the calcium content of the blood by the suggestion of excitement or quieting influences under hypnosis; but again, no skin correlation despite the interest in calcium metabolism for dermatology, is suggested. Both Dunbar's[32] studies of the literature and that of Stokes, Kulchar and Pillsbury[98] failed to find any report of significant general metabolic influence involving acid base equilibrium in urticaria.

Studies of the Pruritus Mechanism. The recent literature, such as it is, continues to emphasize the sympathetic mechanism of itching. Brack,[14] in an extended and involved consideration of the mechanism of itching, draws a sharp distinction between a species of threshold susceptibility to itching (Juckbereitschaft) and actual itching itself. He points out that there is a normal threshold of capacity for itching present in practically all persons, and that it is capable of proceeding towards abnormality or heightened sensitiveness in the direction of either sympathetic or parasympathetic abnormality. His presentation contains interesting comments on the production of itching by slight invisible vasomotor changes in the skin, and correlates itching with the hemoclasic crisis in what he apparently considers an important etiologic relationship. The predisposing causes of itching work chiefly in the field of the Juckbereitschaft, and are often both more numerous and quite distinct from those responsible for the actual itching. In view of this clear separation of the itch problem into two subdivisions, Goldsmith's[40] observations on the clinical side in a study of dermatoses in patients with nervous diseases and those without are interesting. He points out that pruritus depends upon peripheral perceptors both for pain and touch; that itching is received centrally in the thalamus, the cortex apparently having little or nothing to do with it. He mentions the demonstration of central or thalamic itching in cases of thalamic tumor without peripheral manifestations. He further points out that there constantly occur in the normal skin slight itching or pricking sensations (minor expressions of the Jucksbereitschaft?) and that the degree of attention available for them is generally so slight that they pass unnoticed, and need to be greatly intensified in order to enter consciousness. His point that it is sometimes not the sensation of itching that is intensified but the attention, is extremely well taken. The most recent contribution on the condition is that of Bickford[11] who, on the basis of a study of histamine reaction in the skin, also points out that itching phenomena can be grouped into two categories: the actual itch itself which occurs at the site of the stimulus, and "itchy skin," which is the sensory reaction of the surrounding uninvolved area. Itchy skin, which may perhaps be compared to some extent to the Jucksbereitschaft of Brack[14] arises through a local axonic pathway, separate from that which is responsible for hyperalgesia and for the vascular flare. Nerves responsible do not, he believes, belong to the sympathetic system. The itchy skin sensation may be abolished by a degree of asphyxia which leaves spontaneous itching unaffected. A similar dissociation may be produced by cooling and nerve shock. This,

he believes, indicates that the nerves carrying the two sensations are separate. The sensation of tickling shows a close association with that of itchy skin in his experiments. Spontaneous itching is not felt at the point at which pain to the prick of a pin is detected. The pain of tickling, spontaneous itching and itchy skin, are all conveyed in the anterolateral tracts of the cord, since they disappear when this is divided. A condition of the skin in which itching is inhibited is described. Inhibition is central in origin and probably produced through the pain nerves.

Milian,[73] in a recent review of the nature of eczema, argues from clinical observation and theoretical grounds, that itching must be not of peripheral but of central origin, arising in the sympathetic bulbomedullary centers. The associated capillary dilatation, edema and secondary vesiculation are related to abnormal function of the sympathetic nervous mechanism in its threshold susceptibility to itching. Lortat-Jacob[60] demonstrates the definite association of the sympathetic nervous system and pruritus, erythema, and vesiculation in the background of contact allergy. His case, a 50-year-old woman, who had a more or less generalized eruption since 1929, had worked with synthetic vanilla since 1925. The patient gave a positive patch-test to vanilla on the left arm but not on the right. She was then given an intradermal test which evoked generalized itching and when pilocarpine was administered her eruption extended to the point of severe generalization. She was then given atropine, which caused the eruption to disappear, and the patch-test to the supposedly offending substance to become negative.

Central (Thalamic and Other) Mechanisms. Little advance beyond the scanty contributions of central neurophysiology reviewed by Stokes, Kulchar and Pillsbury[98] (1935) has appeared in subsequent literature on the skin. The observations on choligenic urticaria associated with rage and other emotions probably come the nearest to suggesting the validity of the central mechanism with a peripheral neural pathway. The medulliadrenal syndrome of Cannon[20] is probably still the best organized concept with possible cutaneous correlates in the literature. A thoroughgoing and admirable technical review of hypothalamic correlation by Grinker,[42] Ingram,[53] and Ranson[78] mentions not a single cutaneous expression of midbrain disturbance. In fact, the concept of centers itself still seems far from being established and influences such as fear, which are well recognized in the asthma field, for example, appear from physiologic studies to have not centers, but an unusually diffuse functional mechanism in the central nervous system. Bard[6] demonstrates that the function of the cortex is primarily that of a damper or inhibitor, rather than an excitor of the discharge. Thus the nocturnal itch crisis and the urticarial and asthmatic outbursts may be conceived as explosions from an area or a focus as the cortical inhibitory influence is suspended. Cannon pointed out how the inhibition of expressions of emotion may be conceived as leading to correspondingly reduced visceral function—as perhaps in the lowered blood pressure, hypochlorhydria, inhibition of gastro-intestinal movement and secretion, asthenia and muscular weakness that accompany the effort to control such emotions—and are a part of the clinical back-

ground of neurodermatitides, vasomotor neuroses, neurovascular instability, and at times urticaria and rosacea. The conditioned reflex, too, could well have further study, for its relation to fear, to asthma, and to the urticarias seems sufficiently established for a psychiatric and psychologic as well as dermatologic approach. Crocker,[22] years ago, described a still classical example of a woman whose urticaria attacks, originally provoked by meeting strangers, were finally brought on by the mere ringing of the door bell.

The study of postencephalitics from the standpoint of cutaneous functional abnormalities, especially of the sweat and sebaceous mechanisms, as suggested by the observations of Haxthausen[47] (though apparently unconfirmed by Rattner[79]) is also a potential study field.

Skin Infections Conditioned by Psychogenous Elements. We have alluded in the discussion of vascular and sweat mechanisms to a probably important group of dermatoses influenced by the emotions through these structural and functional channels. No dermatologist of experience alert to psychoneurogenous factors has failed to observe the emotionally induced exacerbations of fungus and fungus-pyogenic infections of the hands and feet under the influence of emotion and emotional crises. The ups and downs of the intertriginous streptomycoses involving the areas of apocrine gland distribution in the skin can be readily observed in women under emotional and particularly sexual stress. Sulzberger[100] has even gone so far as to suggest, and not unplausibly, that the prevalence of dermatophytosis in those who use locker-rooms, gymnasiums and swimming-pools is not alone a function of the presence of the organism but of the receptive state of those exposed, particularly with reference to hyperhidrosis and nervous tension. Gillespie[38] cured a proved case of fungus eruption of the hands by three interviews in which the patient's abnormal relation to his father was successfully adjusted. Stokes and Sternberg,[97] in discussing the etiologic background of acne, point out the effect of emotional stress on flares of what is an obvious combination of pyogenic and mycotic infection of the skin. They suggest on clinical evidence that a combination of vasomotor congestive or flush effect with the broadening of the allergic base of the individual under emotional stress is the probably etiologic mechanism. The flush or blush mechanism in particular, in its ability to maintain long-standing hyperemia of the face, unquestionably materially influences the infective phases of the rosacea syndrome, as well as of acne and, even as suggested by Stokes and Callaway,[94] of the recurrences and severity of lesions of chronic erythematous lupus.

Allergic and Psychoneurogenous Correlation in the Skin. The skepticism or indifference of American allergists to the possible psychoneurogenous correlations of allergic phenomena developed by German and British observers in the case of asthma is well illustrated by the total absence of articles or reference to psychoneurogenous correlates in literature reviews in one of the most important American journals of allergy. The work of Fock,[36] Moos,[75] Römer and Kleemann,[83] Laudenheimer,[66] and Hansen[43] should be applied to the allergic background of the eczema phase of the eczema-asthma-hay fever complex as well as other dermatoses. Hansen,[43] after critically reviewing the literature

and his own experience, denied to any form of psychotherapeutic approach the ability to alter the fundamental allergic background, and cited as evidence patients who had lost their symptomatic reactions to their allergens without losing their positive cutaneous tests. A much more crucial type of evidence for the influence of the psychogenous in allergic skin reactivity appeared with the work of Diehl and Heinichen.[29] Their ability to change the wheal reaction to an allergen in controlled conditions under hypnosis has now been confirmed by the observations of Marcus and Sahlgren[71] who, in a 36-year-old female psychopath, succeeded in demonstrating that her cutaneous reactivity to a linoleum extract, to which she was sensitive, could be inhibited almost completely by suggesting under hypnosis that the injected allergen was another substance. The same inhibitions were obtained in the case of pollen extract, and it was found possible to inhibit the tuberculin reaction. A further study of dermographism in her case demonstrated that the dermographic wheal could be enlarged or suppressed under hypnosis. Kartamischew[56c] describes a 41-year-old woman with malaria who was intolerant to quinine, plasmochin, euchinin, developing urticaria 4 hours after administration. This could be cleared almost immediately with morphine, which led the observer to the belief that the effect was psychic. Under hypnosis the patient was given quinine and told that it was salol, whereupon no urticaria appeared. The susceptibility to quinine was thereupon abolished by suggestion. It must be confessed that Kartamischew's remarkable efficiency with hypnosis, as described in other papers, inspires one with a desire for confirmation of these remarkable observations by other workers.

It is proposed to continue the subject in a subsequent review with an enumeration of the dermatoses currently accepted as having marked psychoneurogenous components, including a brief statement on each; with a consideration of psychotherapy, psychoanalysis, hypnosis, and suggestion under anesthesia in the treatment of the psychoneurogenous element and with a critique of current work and literature in this field.

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